ACTA RADIOLOGICA
EDITA IUSSU SOCIETATUM RADIOLOGICARUM
DANIAE, FENNIAE, NORVEGIAE ET SUECIAE

VOL. 55 APRIL 1961 FASC. 4

DEFORMATION OF THE RECTO-SIGMOID JUNCTION IN PELVIC ENDOMETRIOSIS

by

GEORG THEANDER and LENNART WEHLIN

External endometriosis is a fairly common condition characterized by the extrauterine growth of endometrial tissue or possibly metaplastic tissue resembling endometrium. Circumscribed tumefactions may develop ('endometriomas', 'chocolate cysts'), but more often the process invades contiguous tissues with the formation of almost pathognomonically firm and rigid adhesions as well as a marked degree of puckering and scarring. The pelvic peritoneum, recto-vaginal septum, rectum and sigmoid colon are clinically important sites of predilection. Despite the infiltrative mode of growth the mucosa of the rectum and sigmoid is, however, seldom invaded and rectal bleeding is therefore rare.

Clinical and roentgenographic examinations are often insufficient to establish the diagnosis pre-operatively. Pelvigraphy may reveal membranous adhesions or obliteration of the recto-uterine fossa, but the findings are seldom conclusive. Roentgen examination of the bowel may disclose endometriomas of this organ as well as any constrictions resulting from the more diffuse type of growth, but such lesions may be difficult to distinguish roentgenographically from true neoplasms or inflammatory conditions. LILJA's observation (JOSEFSSON 1939) of an increase in the strangulating effect of endometriosis on the bowel during the menstrual period is important in this respect; unfortunately, however, the sign seems to be demonstrable only exceptionally. Despite the in-

From the Roentgendiagnostic Department (Director: Prof. Sölve Welin), Malmö Allmänna Sjukhus, Malmö, Sweden. Submitted for publication 4 August 1960.

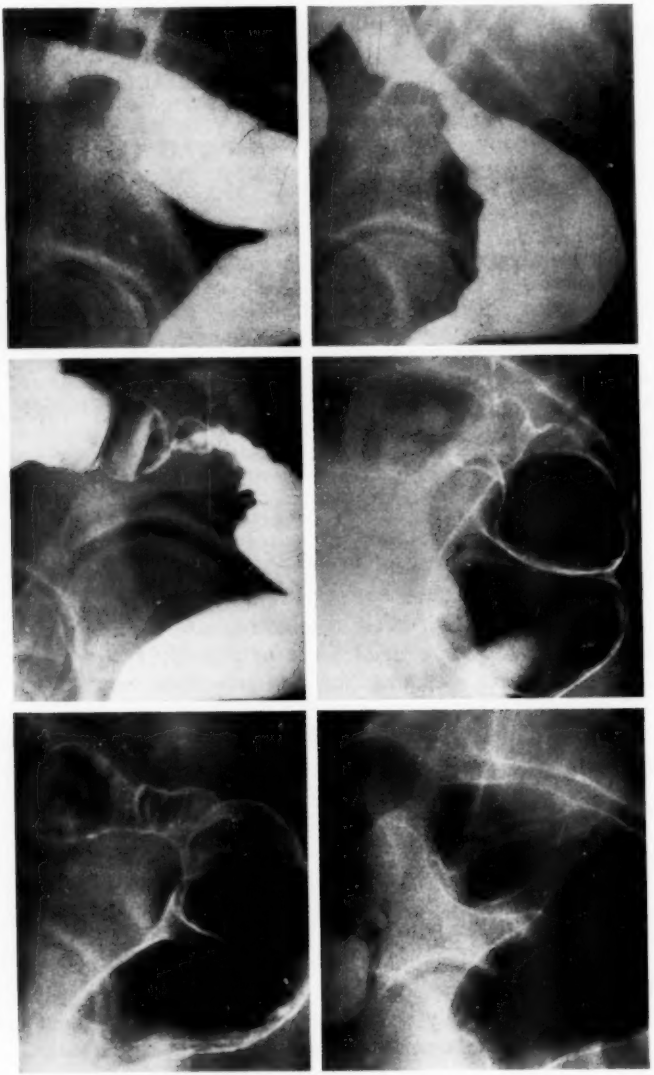
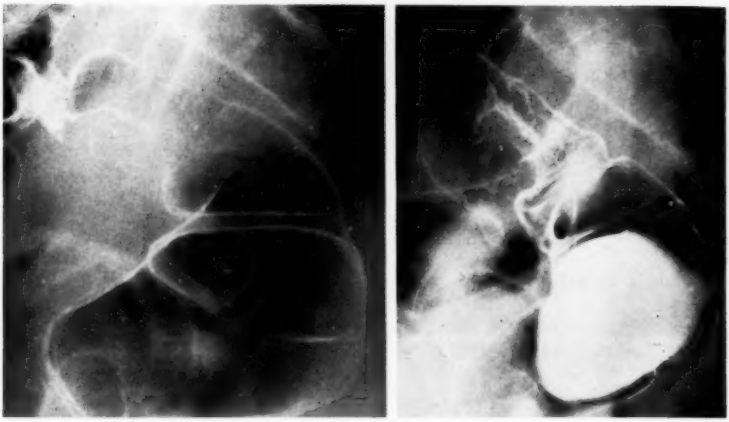


Fig. 1. Deformity of recto-sigmoid junction in 6 women with pelvic endometriosis. Lateral views.

Fig. 2. Primary carcinoma at recto-sigmoid junction in 4 patients. Lateral views. Deformity somewhat similar to that in figs 1 and 3, but with mucosal infiltration.

creasing roentgenologic interest in endometriosis of the colon and rectum (Jenkinson & Brown 1943, Culver & Caldwell 1951, Wietersen & Balow 1957, Boles & Hodes 1958, Culver, Pereira & Seibel 1958, Spjut & Perkins 1959), it is still widely believed that the roentgen appearances of the condition are uncharacteristic and of little help in establishing the diagnosis in clinically doubtful cases.

A peculiar deformity of the recto-sigmoid junction is sometimes present in pelvic endometriosis and is as a rule demonstrable only in the lateral view (Figs 1 and 3). It affects the anterior wall of the bowel below the sacral promontory or, to be precise, at the level of or closely above the superior rectal valve. It appears as a blunt transversal ridge, about 2 to 4 cm in breadth, which projects backwards into the lumen and thus seems to exaggerate the normal bend of this part of the wall. The ridge is rounded and more or less distinctly demarcated in profile, but as a rule its surface is not quite smooth; one or more



a b

Fig. 3. Deformity of recto-sigmoid junction in lateral views: after removal of ovarian carcinoma and radiotherapy (a), and in terminal ileitis with pelvic adhesions (b).

small wrinkles may be seen to continue laterally and dorsally as transverse folds of the bowel wall. The ridge is resistant to any attempts to distend the bowel by instillation of contrast medium or insufflation of air, and it usually prevents passage of a sigmoidoscope. Since the deformity seems to have received little attention in the literature, a study of its occurrence and significance was thought to be of interest.

Material and Method. The study was based on observations made in 8 women with pelvic endometriosis, 176 women and 181 men with primary carcinoma of the bowel, and 169 women and 171 men selected at random from patients admitted for various reasons but not known to have carcinoma of the bowel or endometriosis. In all of these 705 patients the bowel had been examined roentgenographically at least once, and then with few exceptions with the double contrast method used as a routine in our department (ANDRÉN, FRIEBERG & WELIN 1955, ANDRÉN & FRIEBERG 1956). The films taken at those examinations were re-examined for the peculiar deformity described above, and essential clinical and histologic data were extracted from available records.

Results

The deformity under consideration was present in 6 of the 8 women with pelvic endometriosis (Fig. 1). In these 6 and in one of the others operation revealed firm adhesions of pelvic structures including the uterus and the anterior surface of the bowel, whereas in the remaining case the lesions were limited

a

b

Fig. 4. Same case as in fig. 3b, at operation (a), and postoperatively (b). a) Folding of bowel wall and contracted adhesions traversing recto-sigmoid junction. b) Persistence of deformity. Metal clips at recto-sigmoid junction and in recto-uterine fossa.

to a few cysts, the size of a pin-head, in the pelvic serosa. A circumscribed endometrioma at the recto-sigmoid junction was found in 2 cases only. In 4 of the 6 patients with the deformity the bowel was examined roentgenographically after the operation, which included salpingo-oophorectomy on one or both sides as well as supravaginal amputation or total removal of the uterus in all cases but one. In one of the 4 cases small excisions of tissue were also made from the bowel wall at the recto-sigmoid junction; in this case, but not in the others, the deformity was absent postoperatively though the main part of the recto-sigmoid infiltrate had not been removed.

The deformity was extremely less common in patients without known endometriosis. Of the 357 patients with primary carcinoma of the bowel, the neoplasm was situated at the recto-sigmoid junction in 53, but only 4 of them presented a deformity somewhat similar to that observed in pelvic endometriosis (Fig. 2). In these, the true nature of the condition was apparent from mucosal infiltration in the deformed segment of the bowel wall. Two of the remaining 340 patients studied showed the deformity under consideration. One of them (Fig. 3a) had been treated with bilateral salpingo-oophorectomy and radiotherapy for an ovarian carcinoma; the deformity was absent pre-operatively but appeared during the postoperative course with the development of a tender retro-uterine tumefaction. In the other patient (Fig. 4) the deformity was caused by an inflammatory reaction of the pelvic peritoneum to a condition of terminal ileitis. At operation, firm adhesions covering the anterior

UNIVERSITY OF MICHIGAN LIBRARIES

surface of the bowel at the recto-sigmoid junction were found to keep this part of the bowel wall in a state of rigid puckering with fixed transverse folds (Fig. 4a). There was no obliteration of the recto-uterine fossa, and the position of the recto-genital septum was definitely lower than that of the recto-sigmoid junction. To facilitate orientation on subsequent roentgenographic examination, metal clips were fastened at the recto-sigmoid junction and in the floor of the recto-uterine fossa. On re-examination 4 weeks after operation, the deformity of the bowel wall was still demonstrable (Fig. 4b).

Discussion

It is apparent from the present material that the deformity of the recto-sigmoid junction under consideration is fairly characteristic in women with pelvic endometriosis but not pathognomonic of this disease. Several kinds of pathologic processes outside the rectum may deform this organ at various levels by causing a ridge-shaped protrusion of part of its wall into the lumen. Ever since the description by BLUMER (1909) of such protrusions as 'rectal shelfs', the condition is usually referred to as a 'shelf tumour' irrespective of its actual nature. In women it is most often due to various lesions of the genital system (BUIE, JACKMAN & VICKERS 1941).

HULTBORN, MORALES & ROMANUS (1955) published a roentgenographic study of the rectum in 11 patients with a 'shelf tumour', including 3 women in whom the condition was caused by pelvic endometriosis involving the rectal wall. No distinction was made by these authors between the different types of deformity observed, but, judging from the illustrations and descriptions given, the recto-sigmoid junction presented the abnormal shape under discussion in at least 2 of the 3 women mentioned and probably also in one man with pelvic metastases from a pancreatic carcinoma. The factor essential for the development of the 'shelf tumour' was thought to be a pathologic fixation of the uppermost part of the recto-genital septum rendering possible a backward protrusion of the anterior rectal wall by this structure. Since, however, the septum in one of our cases was not at the same level as the deformity (Fig. 4b), this explanation for the 'shelf' does not seem to be valid. The deformity under discussion would appear to be more likely due to fibrous contraction of adhesions at the recto-sigmoid junction.

In general, shrinkage of tissue covering any segment of the bowel must inevitably result in permanent folding of the part of the bowel wall adherent to such tissue. If only, or mainly, the anterior wall is affected, the longitudinal component of the contraction will probably be predominant and give rise to a forward bending of the wall as well as a transverse arrangement of the resultant folds. Such a course of events is apparently favoured by the anatomic conditions characteristic of the recto-sigmoid junction, namely, an anterior curvature and a limitation of the serosal covering to the anterior surface.

As matter of fact, firm adhesions and transversal folding of the bowel wall at t recto-sigmoid junction were observed at operation in the case of terminal ilei included in the present material (Fig. 4a). Judging from an illustrative dia am given by HULTBORN, MORALES & ROMANUS similar findings were ma by them in the man with pelvic metastases from a pancreatic carcinoma refe ed to above. In pelvic endometriosis, the tendency of the adhesions to und go fibrosis and to contract is conspicuous and has been pointed out by mar authors; even the consequent folding and angulation of the bowel wall has been observed (TAGART 1959).

The assumption that the deformity is due to contraction of recto-sigmoid adh ions would explain the roentgenographic appearances of the deformity as well as its location and common occurrence in pelvic endometriosis. It would also explain the disappearance of the deformity after incision of the anterior wall of the affected segment of the bowel as observed in one case reported above. If dependent on mucosal folding, as we have presumed, the deformity will be absent in spite of abundant pelvic adhesions if the latter do not contract sufficiently or if their longitudinal fibres are cut.

In view of the above observations other pathologic conditions causing contracting adhesions in the pelvis, e. g., fibrosis following infections or radiotherapy must also be considered in the establishment of a differential diagnosis. However, the most important task of the roentgenologist is to distinguish the deformity from infiltration caused by primary carcinoma of the bowel. The difficulty encountered in this decision is emphasized by the fact that in 4 of our cases the deformity caused by endometriosis was first erroneously believed to be due to a primary carcinoma. Review of the 357 cases of the latter disease included in the present study strengthened, however, our opinion that a technically satisfactory roentgen examination of the bowel will practically always provide sufficient information for a correct diagnosis.

SUMMARY

The recto-sigmoid junction was studied roentgenographically in 705 cases to determine the diagnostic significance of a deformity observed in that part of the bowel in 6 out of 8 cases of pelvic endometriosis. Contraction of serosal adhesions appeared to be responsible for the development and the characteristic appearance of the deformity.

ZUSAMMENFASSUNG

Die Gegend des Überganges vom Rectum zum Sigmoideum wurde in 705 Fällen röntgenologisch studiert, um die diagnostische Signifikanz einer Deformität festzustellen, die bei 6 von 8 Fällen mit Beckenendometriose in diesem Darmabschnitt beobachtet worden ist. Kontraktion von Serosaadhäsionen schienen für die Entwicklung und das charakteristische Aussehen der Deformität verantwortlich zu sein.

UNIVERSITY OF MICHIGAN LIBRARIES

RÉSUMÉ

Les auteurs ont étudié radiographiquement dans 705 cas la jonction recto-sigmoïd ne pour déterminer la valeur diagnostique d'une déformation de cette partie de l'intestin obs vée dans 6 cas sur 8 d'endométriose pelvienne. C'est la rétraction d'adhérences péritonéal qui paraît être la cause de l'apparition et de l'aspect caractéristique de cette déformation.

REFERENCES

ANDRÉN, L. and FRIEBERG, S.: Roentgen diagnosis of the rectum. Gastroenterology 31 (1956), 566.

— — and WELIN, S.: Roentgen diagnosis of small polyps in the colon and rectum. Acta radiol. 43 (1955), 201.

BLUMER, G.: The rectal shelf: a neglected rectal sign of value in diagnosis of obscure malignant and inflammatory disease within the abdomen. Albany med. Ann. 30 (1909), 361.

BOLES, R. S. and HODES, PH. J.: Endometriosis of the small and large intestine. Gastroenterology 34 (1958), 367.

BUIE, L. A., JACKMAN, R. J. and VICKERS, P. M.: Extrarectal masses caused by tumours of the recto-uterine or recto-vesical space. J. Amer. med. Ass. 117 (1941), 167.

CULVER, G. J. and CALDWELL, M. V.: Endometriosis of the rectosigmoid. J. Canad. Ass. Radiol. 2 (1951), 6.

— PEREIRA, R. M. and SEIBEL, R.: Radiographic features of rectosigmoid endometriosis. Amer. J. Obstet. Gynec. 76 (1958), 1176.

HULTBORN, K. A., MORALES, O. and ROMANUS, R.: The so-called shelf tumour of the rectum. Acta radiol. (1955) Suppl. No. 124.

JENKINSON, E. L. and BROWN, W. H.: Endometriosis; a study of one hundred and seventeen cases with special reference to constricting lesions of the rectum and sigmoid colon. J. Amer. med. Ass. 122 (1943), 349.

JOSEFSSON, H.: Contribution to the diagnosis of strangulating endometriosis in the sigmoid colon. Acta obstet. gynec. scand. 19 (1939), 256.

LILJA, B.: Quoted by JOSEFSSON (1959).

SPJUT, H. J. and PERKINS, D. E.: Endometriosis of the sigmoid colon and rectum. Amer. J. Roentgenol. 82 (1959), 1070.

TAGART, R. E. B.: Endometriosis of the large intestine. Brit. J. Surg. 47 (1959), 27.

WIETERSEN, F. K. and BALOW, R. M.: Colonic endometriosis: roentgenologic aspects. Radiology 69 (1957), 839.

FR[illegible] THE ROENTGEN DEPARTMENT (DIRECTOR: PROF. GREGERS THOMSEN), DEPARTME[illegible] OF SURGERY R (DIRECTOR: PROF. F. THERKELSEN) AND DEPARTMENT OF SURGE[illegible] D (DIRECTOR: PROF. E. HUSFELDT), RIGSHOSPITALET, COPENHAGEN, DENMARK.

RADIOLOGIC EVALUATION OF FUNNEL CHEST

by

OLE G. BACKER, S. BRÜNNER and V. LARSEN

An assessment of the amount of depression of the sternum in funnel chest is generally based either upon the depth of the funnel or upon the minimum distance between the vertebral column and the posterior surface of the body of the sternum. Since, however, the majority of the patients subjected to operation are children, absolute measurements are inapplicable in analysing the late results of the corrective procedures.

The following two relative measurements have proved of value in the radiologic evaluation of the primary and secondary results of operation.

1. *Fronto-sagittal index.* This ratio indicates the percentage relation between the maximum internal frontal diameter of the chest and the minimum sagittal diameter measured from the anterior surface of the vertebral column to the nearest point on the body of the sternum.

2. *Vertebral index.* This indicates the percentage ratio between the minimum sagittal diameter of the chest, measured from the posterior surface of the vertebral body to the nearest point on the body of the sternum, and the sagittal diameter of the vertebral body at the same level (Fig. 1).

Submitted for publication 16 September 1960.

UNIVERSITY OF MICHIGAN LIBRARIES

Fig. 1. Lateral view of patient with moderate funnel chest. Arrows indicate the measurements used in calculating the vertebral index.

Control series

The normal range of these indices and their relation to sex and age were studied in a normal series of 197 males and 248 females, a total of 445 subjects, almost equally distributed in the 5-year age groups from 0 to 25 years.

Fig. 2 gives the distribution of the fronto-sagittal index in the total normal series. The mean value and dispersion were calculated for each one-year age group. The variation around the solid average curve is illustrated by the two broken lines traced at a distance of twice the dispersion. The area between these two curves covers 95 % of the observations. As no significant sex differences were found, the series were considered together. The index fell abruptly during the first 5 or 6 years of life, after which it remained practically unchanged, around a mean value of about 46, throughout the remainder of the growth period.

Fig. 3 shows the corresponding distribution, average curve, and 95 % range of the vertebral index in the total normal series. There was no significant sex difference. During the first 6 years of life the index increased perceptibly, after which it remained at about 20 throughout the remainder of the growth period.

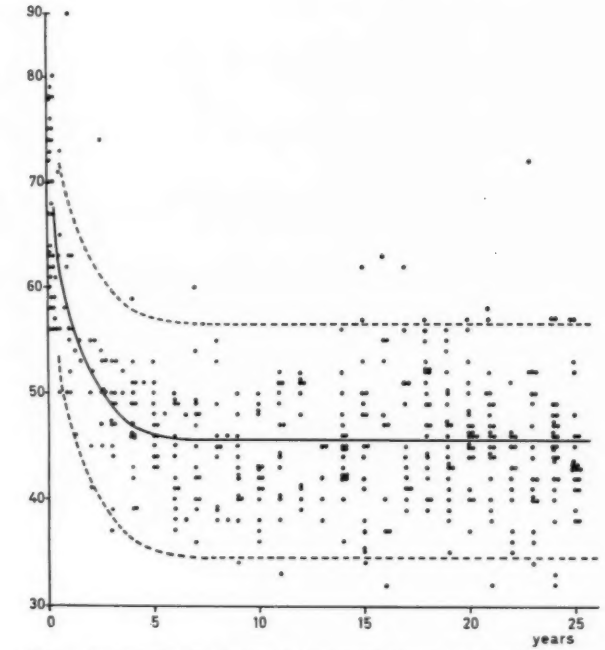


Fig. 2. Fronto-sagittal index in the normal series (445 subjects). The solid line represents the mean curve. The 95 % range lies between the broken lines.

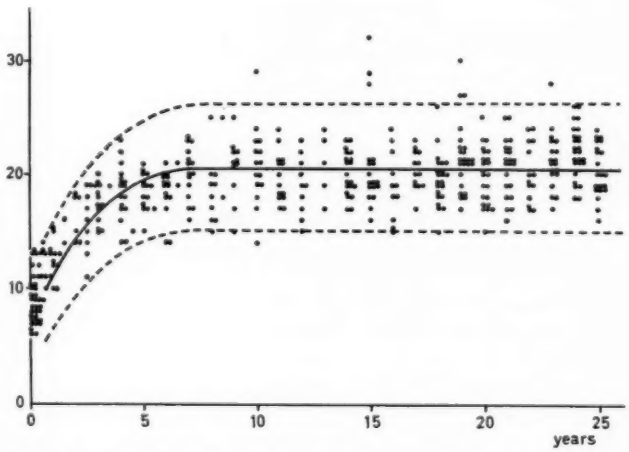


Fig. 3. Vertebral index in the normal series (445 subjects). The solid line represents the mean curve. The 95 % range lies between the broken lines.

UNIVERSITY OF MICHIGAN LIBRARIES

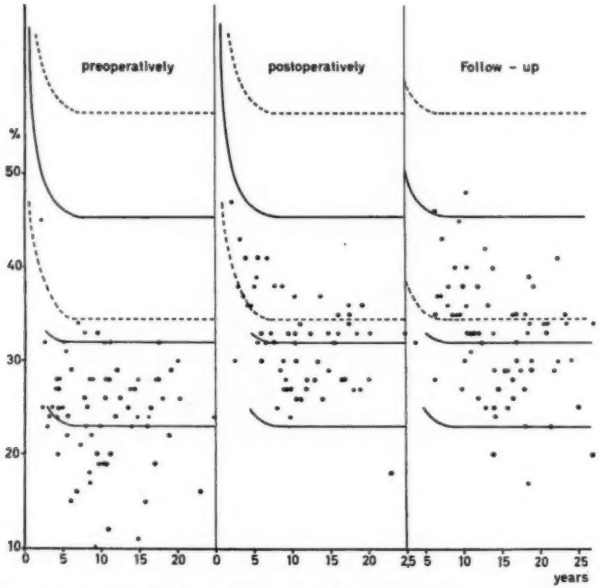


Fig. 4. Fronto-sagittal index for the operation series: pre-operatively, post-operatively, and at follow-up. The normal values are indicated by the mean curve and the 95 % range. The two curves at the bottom indicate the severity of the funnel chest. From bottom to top: severe, moderate and mild cases.

Practical application

The applicability of the indices was tested and their relation to the absolute measurements was fixed in a series of 74 patients operated upon for funnel chest during the period 1948—1958 and followed up for an average of 4.2 years (0.8 to 10.3 years).

In funnel chest the fronto-sagittal index is below normal and the vertebral index above normal. After reduction of the sternum the two indices show a rise and a fall respectively. Where the primary operative result is good, the indices are brought within the normal ranges. A recurrence manifests itself in a renewed fall in the fronto-sagittal index and a rise in the vertebral index, as compared with the values found immediately after the operation.

Figs 4 and 5 set out the indices in the series of patients with funnel chest, before operation, immediately following operation, and at follow-up. The normal average curve and the 95 % ranges are plotted in the figures.

The correlation between the percentage increase in the sterno-vertebral distance and changes in the two indices are shown in Figs 6 and 7.

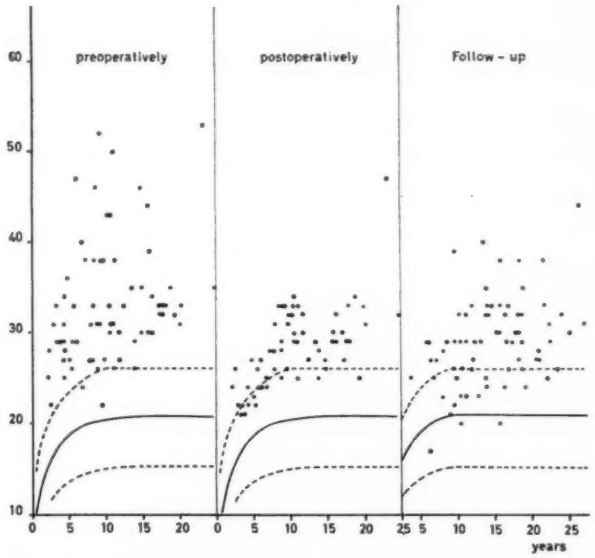


Fig. 5. Vertebral index in the operated series: pre-operatively, postoperatively, and at follow-up. Normal values indicated by the mean curve and the 95 % range.

The normal average distance from the vertebral column to the sternum is considered to be about 10 cm in adults (according to ROESLER: 10.3 cm in males and 9.2 cm in females). According to FABRICIUS et coll. a funnel chest in an adult is 'severe' if the distance between the vertebral column and the sternum is 5 cm or less and 'moderate' if this distance is between 7 and 5 cm. The corresponding border-line values of the fronto-sagittal index may be deduced on this basis. The material was divided into 28 severe, 35 moderate, and 7 mild cases, by plotting in Fig. 4 two curves parallel to the normal average curve, with ordinates of 50 % and 70 % respectively. One case fell within the normal range.

The secondary results of operation in the 74 operated cases are summarized on p. 255. It may be seen that 20 (27 %) were unchanged or worse, 28 (38 %) were corrected to within the normal range, and the remaining 26 cases (35 %) were markedly improved. Furthermore, it appears that the results were most satisfactory in cases of severe funnel chest. Of 28 severe cases 25 were improved, while in 3 the condition postoperatively was unchanged (11 %). Among the moderate and mild cases, no improvement occurred in 31 % and 71 % respectively.

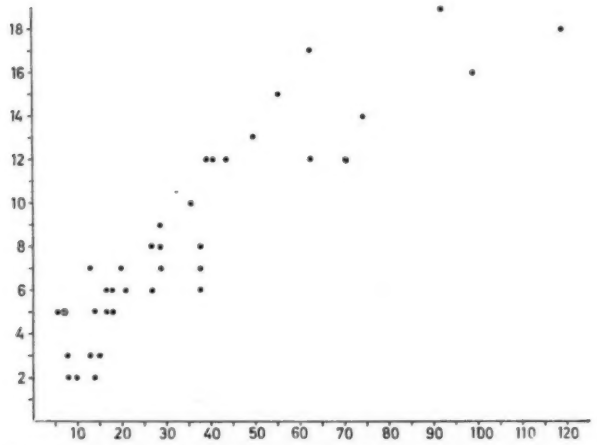


Fig. 6. Correlation between percentage increase in sterno-vertebra distance (abscissa) and increase in fronto-sagittal index (ordinate)

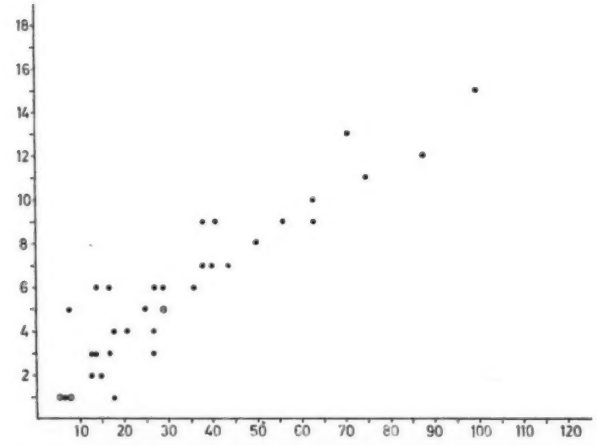


Fig. 7. Correlation between percentage increase in sterno-vertebral distance (abscissa) and decrease in vertebral index (ordinate).

Pre-operative condition	*Secondary results*	
Severe funnel chest 28 cases	Severe funnel chest	3 cases
	Moderate » »	12 »
	Mild » »	2 »
	Corrected	11 »
Moderate funnel chest 35 cases	Severe funnel chest	1 case
	Moderate » »	10 cases
	Mild » »	10 »
	Corrected	14 »
Mild funnel chest 7 cases	Severe funnel chest	1 case
	Moderate » »	3 cases
	Mild » »	1 case
	Corrected	2 cases
'Normal': 1 case	Normal	1 case
No pre-operative films 3 cases	Severe funnel chest	1 case
	Moderate » »	1 »
	Mild » »	1 »

Displacement of the heart. Cardiac displacement, if any, is generally included in the radiologic evaluation of funnel chest. This displacement may be to one side, generally the left, or in the form of rotation on various axes (vertical, sagittal-horizontal, and fronto-horizontal). Among the 74 patients included in the follow-up, 49 (66 %) had displacement of the heart to the left pre-operatively. Out of these 49 patients 35 had satisfactory correction of the sternum at follow-up, but the displacement of the heart remained unchanged in 18. In other words, the heart remained displaced in half the cases, even despite correction of the sternal deformity.

Discussion

The increase in the absolute distance between the vertebral column and the sternum is applicable in assessing the primary result of operation for funnel chest. It is inapplicable, however, in evaluating the late results, since most of the patients are children. The assessment of the late results has been based up to now on a subjective estimate, and this has made it difficult to compare the different series.

The relative measurements described are well-defined in a normal series and allow objective evaluation of the primary as well as secondary results. This permits a comparison within the same series at different times following operation.

A prerequisite for the vertebral index is a true lateral view; even a slightly oblique projection will make the diameter of the vertebral body too large and the sagittal diameter of the chest too small, so that the index will in turn become too high.

The secondary changes in cardiac configuration and in the hila of the lungs, described by previous authors (ALBRECTSEN 1954, EDLING 1953, EVANS 1946, ERNBERG 1951, FABRICIUS et coll. 1957), are less suited for assessing the result of an operation upon a funnel chest because in many cases these changes persist even after satisfactory correction of the sternum. This was observed in the present series and has previously been described by PALTIA et coll. (1959).

SUMMARY

The primary and secondary operative results in 74 cases of funnel chest were evaluated radiologically by means of two relative measurements of the sternal depression, viz. a fronto-sagittal index and a vertebral index, defined in a series of 445 normal subjects.

ZUSAMMENFASSUNG

Die primären und sekundären Operationsresultate in 74 Fällen mit Trichterbrust sind radiographisch untersucht worden. Man benutzte dabei 2 relative Messungen der sternalen Depression, nämlich einen fronto-sagittalen und einen vertebralen Index, welche man mit Hilfe von 445 Normalpersonen definiert hatte.

RÉSUMÉ

Les auteurs ont établi sur une série de 445 sujets normaux un indice thoracique fronto-sagittal et un indice vertébral permettant de mesurer la dépression sternale. Au moyen de ces deux mesures, ils ont évalué radiographiquement les résultats opératoires immédiats et éloignés dans 74 cas de thorax en entonnoir.

REFERENCES

ALBRECTSEN, S. R.: Tragtbryst (funnel chest). (In Danish.) Ugeskr. Læg. 116 (1954), 905.

EDLING, N. P. G.: The radiologic appearances of the heart, oesophagus and lungs in funnel chest deformity. Acta radiol. 39 (1953), 273.

ERNBERG, T.: The symptom complex in cor planum. Acta med. scand. Suppl. 262 (1951), 51.

EVANS, W.: The heart in sternal depression. Brit. Heart J. 8 (1946), 162.

FABRICIUS, J., DAVIDSEN, H. G. and HANSEN, A. T.: Cardiac function in funnel chest. Dan. med. Bull. 4 (1957), 251.

PALTIA, V., PARKKULAINEN, K. V., SULAMAA, M. and WALLGREN, G. R.: Operative technique in funnel chest. Acta chir. Scand. 116 (1959), 90.

ROESLER, H.: Quoted by Fabricius et coll.

FROM THE ROENTGENDIAGNOSTIC DEPARTMENT (DIRECTOR: PROF. SÖLVE WELIN), UNIVERSITY OF LUND, MALMÖ ALLMÄNNA SJUKHUS, MALMÖ, SWEDEN.

THE DOUBLE CONTRAST METHOD IN ULCERATIVE COLITIS

by

SÖLVE WELIN and FOLKE BRAHME

The last decade has witnessed an increase in interest in the diagnosis and treatment of ulcerative colitis. This is to no small extent due to the introduction of new therapeutic methods and to more active surgery. Experience has shown that the risk of malignant degeneration in the chronic stage of the disease is considerable and that carcinoma arising in cases of colitis is highly malignant and forms early metastases. All workers in this field have been impressed by the poor prognosis. In REIFFERSCHEID's compilation of 22 456 cases of ulcerative colitis only 3.5 % were found to have cancer, but for those who had had colitis for 5 years or more the frequency was 17 % and for those who had had the disease for 15 years it was as high as 25 %. LAGERCRANTZ found a frequency of 33 % in a paediatric series in which the children had had colitis for more than 10 years; CATTELL found that in cases he had operated upon the overall incidence of carcinoma was 7 %, but of those who had had the disease for 9 years or more before the operation malignant lesions developed in one third. COUNSELL and DUKES gave a corresponding frequency of 45.5 %. Some authors even claim that when treatment is confined to non-surgical methods, patients with chronic ulcerative colitis undoubtedly die with undiagnosed cancer, for the symptoms of a neoplasm are also those of colitis. Since colectomy is said to carry an operative mortality of only 6.9 %, many believe prophylactic colectomy to be justified in chronic cases. An early

Submitted for publication 16 September 1960.

operation may alter the natural course of this condition, and more and more clinicians are now inclined to refer their patients for operation at a relatively early stage. According to SLANEY and BROOKE, total colectomy is indicated even if cancer has developed. They had two patients who were alive 7 and 8 years after excision of the large bowel. It is obvious that this tendency places increasing demands on diagnostic roentgenology. Clinicians now wish to have definite information on the nature of any change and preferably whether or not such a change is reversible.

As early as 1912 STIERLIN described the roentgenographic features of ulcerative colitis. Since then many papers on this subject have been published. In the beginning, barium meals and enemas were used but at that time changes could be demonstrated only if they were relatively marked. Later, the examination was extended to include the post-evacuation film, which gives a fair demonstration of the mucosa and therefore constitutes an essential part of the examination.

Reports on the use of the double contrast method in ulcerative colitis are fairly scanty, probably because of the poor results so often obtained. We have only found two authors who have recommended the method, namely FELDMAN and BACON. FELDMAN in his book (1957) says that 'the double contrast enema with air insufflation of the colon is of considerable aid in the study of this condition', and BACON (1958) states 'that the double contrast method is an invaluable aid and is to be strongly recommended in the effort to determine the extent, the severity and the complicating factors not clearly evidenced by the mere administration of barium'.

Other workers in this field express a more or less opposite opinion. According to STEVENSON (1954), for example, the double contrast method will not show pathologic changes in inflammatory processes of the colon, because the air will distend the colon to its normal size and the mucosal detail will be lacking. In his opinion then the method is useless. PANSDORF found it difficult to cleanse the intestine properly and BUCKSTEIN stated that regarding air inflation of the colon in ulcerative colitis a word of caution is essential. There is a definite tendency for these ulcers to perforate, and this tendency may be exaggerated by any effort at gaseous distention. The routine use of such a procedure in this disease should therefore be discouraged; if employed at all, the method should, according to him, be applied only to cases that are well beyond the stage of acute inflammation. KALIL and ROBBINS also refrain from the use of the double contrast method because of the risk of perforation. They stated, however, that in those cases in which air was by chance present or had been introduced the stippling was particularly clear. In 1959 DICK, BERRIDGE and GRAYSON published an extremely detailed investigation of the pathologic basis for the roentgen changes in ulcerative colitis. Their material consisted of 10 patients who had undergone colectomy for ulcerative colitis. These patients had also been examined by the double contrast method and on only one oc-

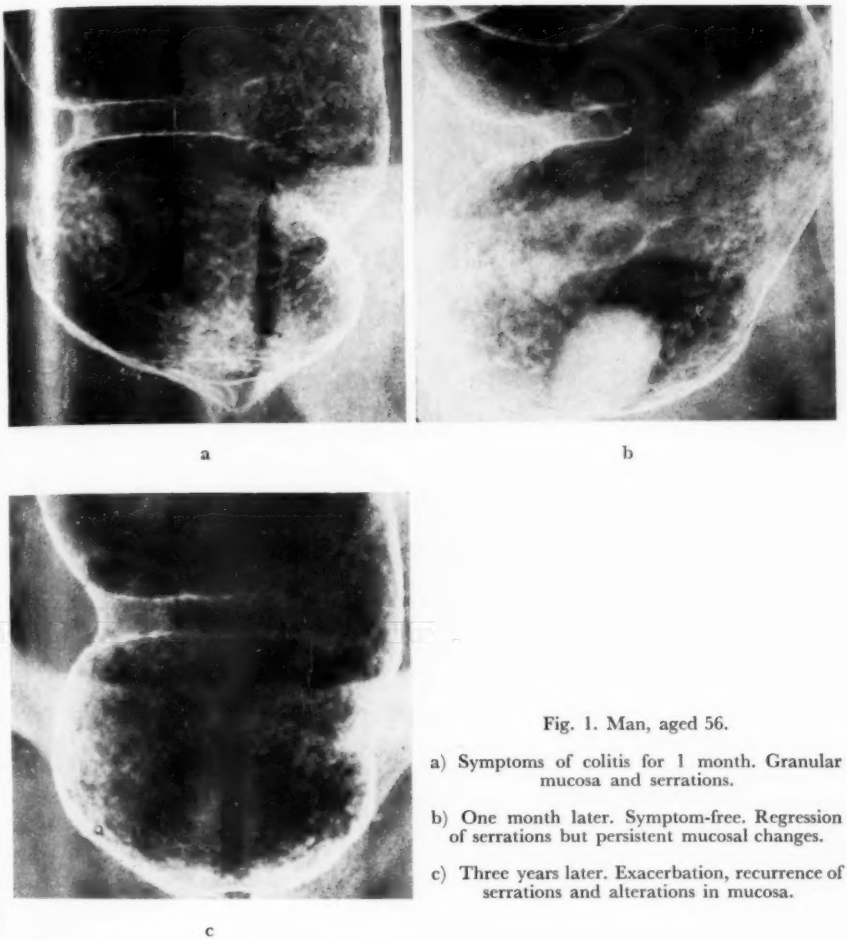


Fig. 1. Man, aged 56.

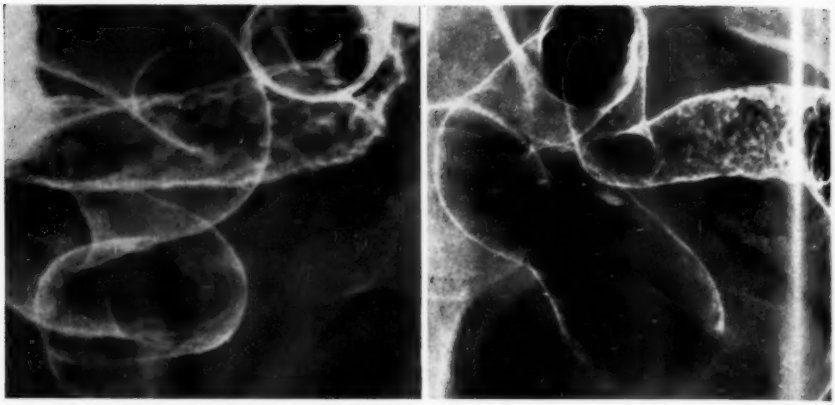
a) Symptoms of colitis for 1 month. Granular mucosa and serrations.

b) One month later. Symptom-free. Regression of serrations but persistent mucosal changes.

c) Three years later. Exacerbation, recurrence of serrations and alterations in mucosa.

casion had the method revealed changes that could not be demonstrated by barium enema or post-evacuation films.

Our modification of the double contrast method described in a number of previous papers has proved extremely efficient and has often yielded information that could not be obtained by previous methods. The diagnosis has become more refined and more reliable and permits of a relatively early diagnosis. It has also been possible to follow the course of the disease much better than previously. Moreover, the examination of patients with ulcerative



a b

Fig. 2. Woman, aged 65. a) Slight mucosal changes in rectum. Incipient pseudopolyposis of sigmoid with ulcerations. b) 4 months later. No symptoms. Total regression in rectum, no ulceration in sigmoid but still changes in the mucosa.

colitis has never produced any complications, and the slight irritation sometimes occurring in association with the examination is often followed by a period of several weeks during which the symptoms are less severe than before the roentgen examination. This might possibly be explained by the tannin in the Clysodrast preparation and possibly also by the barium. One case of acute exacerbation in association with the examination has, however, been observed. We have used the double contrast method routinely since the autumn of 1953 in more than 15 000 cases.

We have modified the preparation of patients with known ulcerative colitis. Patients with an acute exacerbation of their colitis or with colitis in an acute stage no longer receive castor oil the day before the roentgen examination, and usually no cleansing enema. Clysodrast is not added to the enema given on the day of the examination but incorporated in the two barium enemas, the first of which extends up to the proximal aspect of the splenic flexure and the other to about the middle of the sigmoid colon. All patients receive 1 mg of atropine half an hour before the examination.

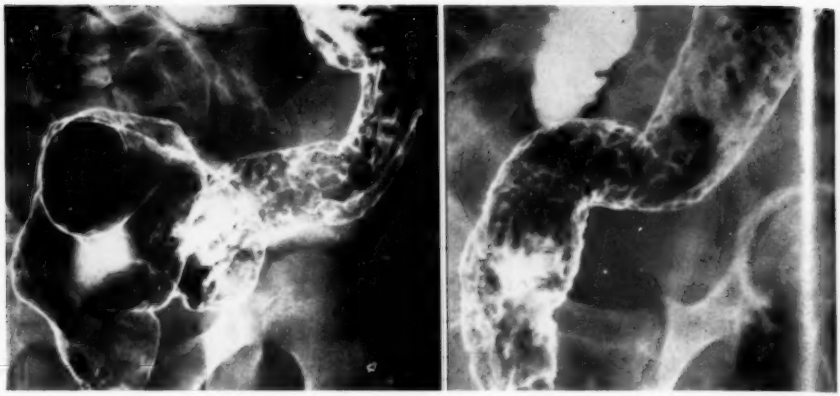
From November 1953 to September 1960 we have found changes suggestive of ulcerative colitis in 160 patients in most of whom the diagnosis was confirmed on proctoscopy, operation or postmortem examination. The diagnosis has, however, not been verified in a few of the unoperated cases in which the ulcerative changes were localized to regions beyond the reach of the proctoscope.

Fig. 3. Male, aged 16. Pseudopolyposis in the descending colon with fairly deep ulcerations.

Fig. 4. Woman, aged 52. Deep ulcerations in transverse colon, in places causing a double outline. Pseudopolyposis.

It has long been known that the inflammatory process may start anywhere in the colon and that in some forms of ulcerative colitis proctoscopy shows nothing pathologic. In such cases only roentgen examination may verify the clinical suggestion. According to the American literature, colitis is localized beyond proctoscopic reach in 8 to 10 % of all cases. In our series the corresponding figure was found to be 13 %. From a pathologic point of view, the process begins with hyperaemia and oedema of the mucosa and can be demonstrated by our method. It appears that the 'indenture sign' described by POPPEL and BERANBAUM represents a later stage with more advanced mucosal alterations, even though the authors claim that it is not due to ulcerations but only represents barium extending in between the rather uniformly swollen mucosal folds. The small mucosal changes demonstrated by the present method are also seen in exacerbations and remissions in patients with slight ulcerations. They will not be visible in barium enema or postevacuation films because the changes are too small.

It is probable that these early cases are responsible for the previous discrepancy between the clinical picture and the roentgen findings, it having often been claimed that the roentgenographic appearance has been normal

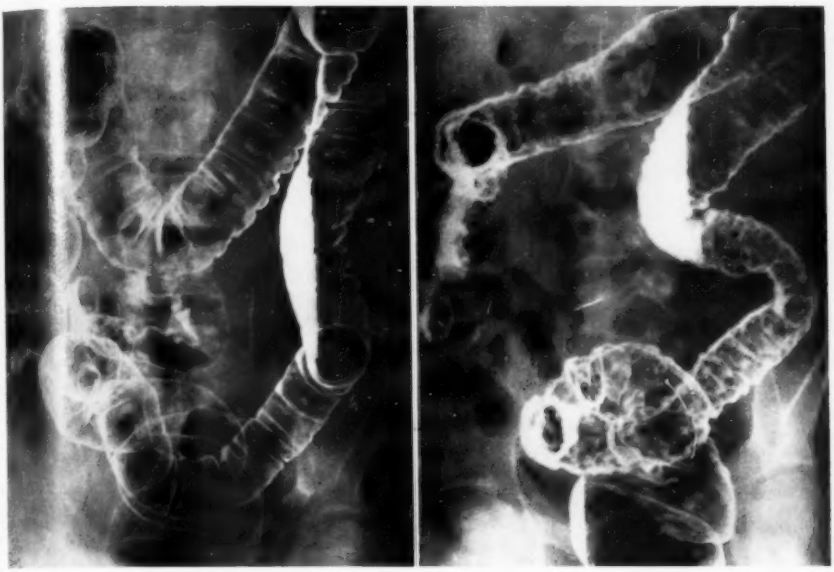


a b

Fig. 5. a) Boy, aged 13. Pseudopolyposis of sigmoid, rectum not involved. b) Man, aged 65. Massive pseudopolyposis in rectum and sigmoid.

in clinically definite cases of ulcerative colitis with positive proctoscopic findings. In RICKETT's material, for example, there was an apparently normal colon on roentgen examination in 60 of 156 patients with clinical evidence of non-specific ulcerative colitis. They explained this by the assumption that the condition may remain a relatively superficial process in many cases with symptoms of long duration. In this connection it might be pointed out that the diagnosis of ulcerative colitis cannot be established roentgenologically unless actual ulcerations can be demonstrated.

We have been able to demonstrate the early change in the mucosa in as many as 23 patients and we have found this refinement of the method to be of great importance. The double contrast film shows a somewhat irregular finely granular surface (Fig. 1). When the disease was localized to the rectum, proctoscopy revealed a somewhat swollen mucosa with a certain tendency to bleeding. The granulation in the mucosa is sometimes coarser and more marked. This may then give the impression of incipient pseudopolyposis and the demarcation between the changes in this stage and the initial stage is vague. This is illustrated in Fig. 2a in which the changes are somewhat more advanced in the sigmoid colon, which also contains ulcerations, than in the rectum. These findings were confirmed on proctoscopy. After 4 months' treatment, during which all symptoms disappeared, roentgen examination showed a considerable regression of the changes. The ulcerations in the sigmoid had by then completely disappeared; only a certain granulation persisted while



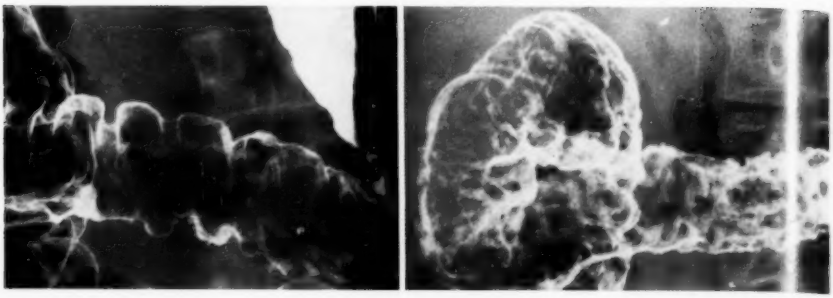
a b

Fig. 6. Man, aged 42. Periodic diarrhoea since 1930. a) Normal roentgenogram. b) 1.5 years later. Pseudopolyposis with several ulcerations, stenosis of ascending colon and caecum.

the rectum had a normal appearance (Fig. 2b). Proctoscopic examination revealed no signs of a pathologic condition.

Ulcerations may develop in the somewhat more advanced cases in which the inflammatory process is no longer localized to the mucosal surface but has penetrated deeper into the intestinal wall. In the beginning they appear as pinpoint- to pinhead-sized tiny serrations along the edge of the bowel (Fig. 1a). These are miliary abscesses which on breaking down produce small ulcers. KALIL and ROBBINS, in particular, stressed the importance of these roentgen findings as an early sign of ulcerative colitis.

If the process progresses it will result in a deepening and widening of the ulcers (Fig. 3). The ulcers may remain limited by the muscularis or they may penetrate through it to form a submuscular abscess giving the 'collar-stud' appearance. If the ulcerations continue to increase in size, and particularly in number, they may cause a double outline in the roentgenogram (Fig. 4). According to KALIL and ROBBINS this is due to a large number of such deep ulcers, the inner wall being outlined by the mucosa, the outer wall by barium contained in the bases of the deep ulcers. DICK, BERRIDGE and GRAYSON,



a b

Fig. 7. Woman, aged 25. Symptoms of colitis for 4 months. a) Granular mucosal relief in transverse colon and serrations. b) 2 months later. Clinical improvement but pseudopolyposis and deeper ulcerations.

who compared the histologic and roentgen findings, found that the double contour is associated with active acute inflammation in which there are islands of inflamed mucosa interspersed with denuded ulcerative areas. The change, demonstrated best by the double contrast method, is probably pseudopolyposis. The method gives much more reliable information than any other on the extent and severity of the lesions. The pathologic basis in the severe, acute phase is said to be islands of non-ulcerated swollen mucosa between deep ulcers; in the chronic stages fibrous tags remain after destruction. In double contrast films the changes appear as a mottled honeycombed and marbled pattern because of the numerous small, rounded formations projecting into the lumen. Pseudopolypi may vary considerably in size (Figs. 3, 5a and 5b) and we have often found it hard to distinguish between granular mucosa and pseudopolyposis.

Some authors claim that it is sometimes difficult to make a differential diagnosis between pseudopolyposis and adenomatosis. HAWKES and SHIELD state, however, that such a differential diagnosis is possible by barium enema examination since cases with pseudopolyposis have lost haustration and have luminal stenosis and mucosal thickening with segmental involvement of the bowel, while in adenomatosis haustration of the colon is normal and there is no stenosis. Since the introduction of the double contrast examination we have had no difficulty in differentiating between the two conditions. In this material we have diagnosed pseudopolyposis in 23 patients, or in 14 %. BARGEN gave a figure of 10 %. How quickly pseudopolyposis can develop is illustrated by the following 2 cases.

Case 1. Man, aged 42, referred for roentgen examination of the large bowel because of rectal bleeding; this showed no evidence of abnormality (Fig. 6a). Proctoscopy revealed a readily bleeding mucosa, which was, however, not swollen. Because of recurrent symptoms

Fig. 8. Woman, aged 24 with symptoms of colitis for 10 years. Typical appearances in chronic stage.

Fig. 9. Woman, aged 46. Dilatation of descending colon and stenosis of rectum.

of colitis the patient was re-examined roentgenologically 18 months later, and advanced changes were seen in the form of pseudopolyposis and deep ulcerations in the sigmoid, and the descending and transverse colon, with shortening and marked stenosis of the ascending colon and caecum (Fig. 6b).

Case 2. Woman, aged 25, who after periods of diarrhoea with a passage of 4 to 5 stools a day for 4 months, was referred for roentgen examination. A double contrast examination showed that the mucosa of the transverse colon here and there was slightly granular and contained numerous small ulcerations (Fig. 7a). The patient responded well to antibiotics and steroids, and the symptoms abated considerably. Roentgen examination two months later, however, revealed deeper lesions and severe pseudopolyposis in the same regions. The process had now also involved the descending colon (Fig. 7b).

Double contrast studies will also give a good impression of the condition of the intestinal wall in the chronic healing stages of the disease in patients with only slight symptoms. The mucosa is often atrophic (Fig. 8). The classical changes with shortening of the intestine, straightening of the flexures, stenosis of the lumen and absence of haustration are also generally evident.

Lamb, Proteroe and Ramsey stress that colonic dilatation is sometimes seen. This dilatation may be general but in some cases is localized to one segment. They emphasize the recognition of dilatation of the colon as attending fulminating ulcerative colitis and Ripstein inclines to the view that a distended

Fig. 10. Woman, aged 38. Complicating fistulae with abscess.

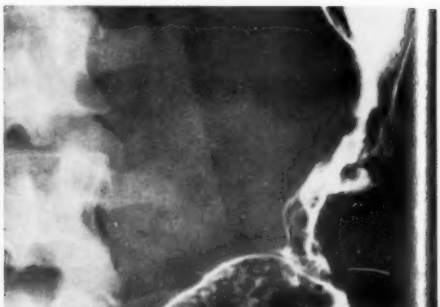


Fig. 11. Man, aged 28. Granular mucosa and cancer of descending colon.

segment of the colon, without small bowel distention, is a sign of impending perforation.

Our series also included such a case of dilatation. The patient had only slight symptoms at the time of the examination; the clinician who had referred the patient for examination believed the disease to be in the healing stage. Examination, however, revealed (Fig. 9) considerable dilatation of the sigmoid and descending colon and the aboral segment of the transverse colon, while the rectum was narrowed. The examination also showed numerous polypous formations, the largest of which were situated in the descending colon.

Practically all authors stress the risk of perforation and formation of fistulae. Our examination method should demonstrate such changes, and in several cases we have been able to distinguish short fistulae from deeper ulcerations. The fistulae sometimes assume considerable proportions (Fig. 10).

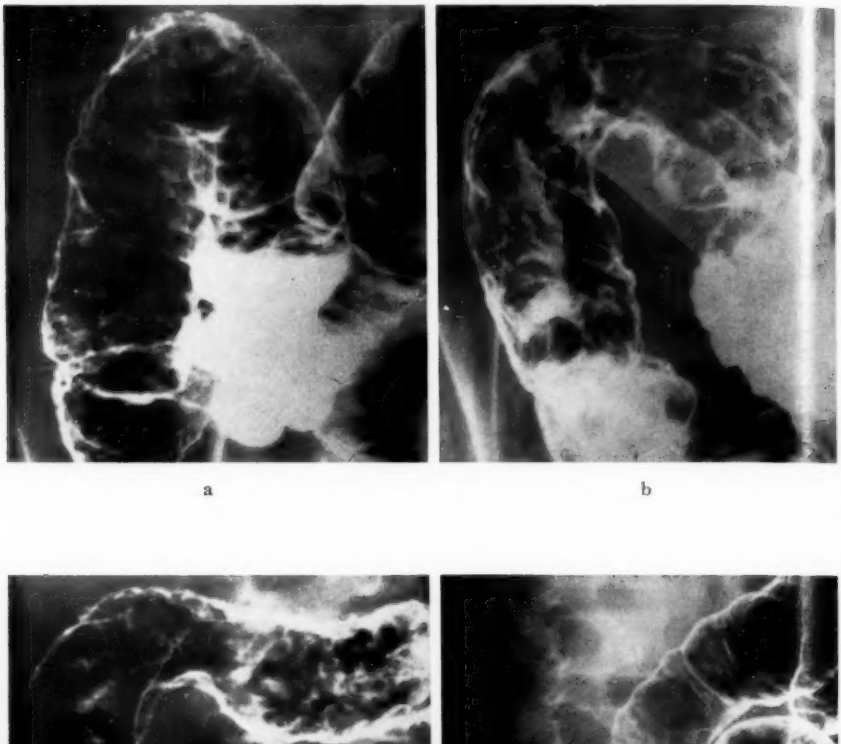
Malignant degeneration is one of the most serious complications of ulcerative colitis, and is also one of those that has received most space in the literature. There appears to be general agreement that this coincidence is of a causal nature and not simply due to chance. There is evidence that the degeneration develops more often in children who have ulcerative colitis and at an earlier stage in patients with ulcerative colitis than in those not so affected. Cancer usually sets in within a phase of the ulcerative colitis that may be described

as a healing stage, but it is still debatable whether the malignant process arise from an atrophic mucosa, pseudopolyposis or in association with malignant degeneration of a polyp. EDLING et coll. state that polyposis, pseudopolyposis or pseudopapillomatosis were certainly not demonstrated in all their cases of cancer and they stress that they do not consider that cancer in ulcerative colitis is usually preceded by the formation of polypi. JOHNSSON and ORR believe that the pseudopolypoid tumours that occur never become true polypi and that they may even regress and disappear. According to SPRATT, ACKERMAN and MAYER, pseudopolypi of ulcerative colitis cannot give rise to carcinomas because, except at their periphery, they lack epithelial cells.

FELSEN and WOLARSKY had previously concluded that this complication developed independently owing to pre-existing adenomas, and COUNSELL and DUKES, who found cancer in 13 of 63 specimens of the colon in cases of ulcerative colitis, made the observation that the malignant lesions often display none of the usual gross features of neoplasm of the bowel, and that malignant cells commonly lurk in strictures with no macroscopic characteristics.

Our series included only 4 cases with malignant degeneration. Two of them had had signs of colitis for 7 and 20 years, respectively; acute ileus was the indication for roentgen examination in one and in the other case a primary tumour was suggested because of the accidental finding of carcinoma of the peritoneum during a hernia operation. In the remaining 2 cases there was no history of colitis. One of the patients had had an abrupt onset with blood-stained diarrhoea, and operation for acute ileus had in the other revealed a ring carcinoma of the ascending colon; subsequent roentgen examination for ascertaining the size of the tumour demonstrated a granular mucosa and small ulcerations in the rectum. Advanced annular tumours were found in all 4 cases. The patient with involvement of the peritoneum (Fig. 11) had a granular mucosa from the rectum to the middle of the descending colon where a 4 cm long stenosis was observed. The distinct border of the cuff-like stenosis and the ragged and rigid mucosa suggested a malignant neoplasm rather than stenosis due to inflammation; if the stenosis is due to inflammation, the outline is usually smoother and the mucosa of a different pattern. BRANCH and SLEDGE, however, claimed that the differentiation between a neoplasm and an inflammatory lesion could not be made pre-operatively and that the presumptive diagnosis in all their 12 instances was carcinoma. Our experience is not sufficient to permit any valid conclusions, but we feel that in such cases double contrast studies may be useful.

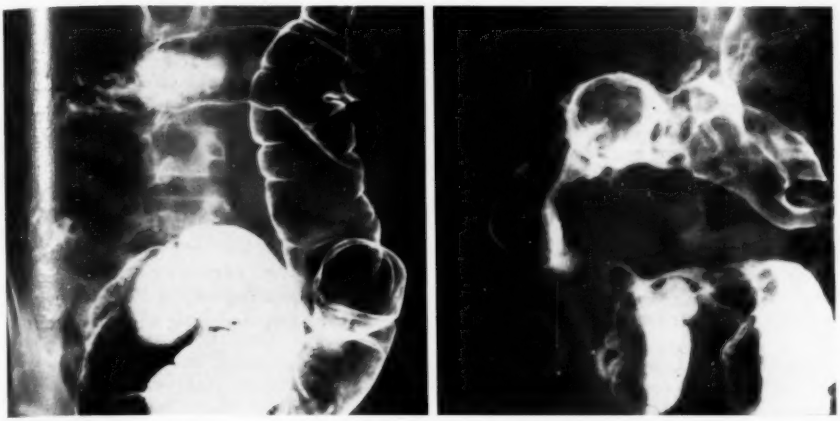
It was, of course, of particular interest to assess the frequency of polypoid tumours in such a colitis series. Apart from the 17 cases with pseudopolyposis in which it was not possible to decide with certainty whether a polypoid new formation was present or not we have demonstrated one or more polypoid tumours in 57 (36.5 %) of our 160 cases. During the same period we have found one or more polypoid tumours in 1 363 cases (12 %) of our complete



a b

c d

Fig. 12. Male, aged 17. Symptoms of colitis for 6 months. a) Incipient pseudopolyposis with slight shrinkage of caecum and ascending colon as well as ulcerations at hepatic flexure. b) About 6 weeks later. No symptoms. Regression of ulceration, progression of pseudopolyposis and shrinkage. c) About 5 months after (b). Exacerbation, pseudopolyposis and continued shrinkage. Recurrent small ulcerations. d) About 3 months after (c). Clinical improvement, continued shrinkage. New ulcerations and alterations of mucosal pattern in descending colon.



a b

Fig. 13. Same case as in fig. 12. a) About 2 months after the examination illustrated in fig. 12d. Clinically as before; considerable progression in ascending colon, complete regression in descending colon. b) About 6 months after (a). Clinical progression in spite of cortisone, development of fistulae. Colectomy performed.

material (12 226 patients). The frequency of cases with polypoid tumours was thus at least three times larger in this colitis series, a fact which does not permit any conclusions but may nevertheless suggest a certain relation between the two conditions.

As mentioned previously, it is now possible to follow the course of the disease fairly closely by double contrast studies. We have done so in many of our cases and found it useful, particularly in the segmental cases where the rectum and sigmoid colon were not involved. There is in such cases often a lack of agreement between the patient's symptoms and the course of the disease as judged from the roentgen findings. Roentgen changes may often progress despite clinical improvement, as exemplified in Figs 12 and 13. The opinion of MONAT, and several others, that the roentgen findings at times fail to reflect the severity of the clinical picture whereas the sigmoidoscopic changes closely follow the clinical course is thus by no means without exceptions. We feel that a periodic roentgenographic and sigmoidoscopic study of the colon is indicated in all cases of long-standing ulcerative colitis, since the course is characterized by exacerbations and remissions. So-called 'cured cases' should also be re-examined at regular intervals owing to the risk of malignant degeneration.

SUMMARY

A material of 160 cases of ulcerative colitis examined by a modification of the double contrast method is reported. This means of investigation has proved more effective than the usual barium enema. The diagnosis of the condition is considered and the common complication of malignant degeneration discussed.

ZUSAMMENFASSUNG

Ein Material von 160 Fällen mit ulzeröser Colitis wird vorgelegt, welches mit Hilfe einer Modifikation der Doppelkontrastmethode untersucht worden ist. Diese Untersuchungstechnik hat sich effektiver als der übliche Bariumeinlauf erwiesen. Die Diagnose der Erkrankung wird erwähnt und die gewöhnliche Komplikation der malignen Degenerierung wird besprochen.

RÉSUMÉ

Présentation d'une série de 160 cas de colite ulcéreuse examinés par une modification de la méthode de double contraste. Cette technique d'examen s'est montrée supérieure au lavement baryté habituel. Les auteurs étudient le diagnostic de cette affection et examinent sa complication fréquente par dégénérescence maligne.

REFERENCES

ANDRÉN, L. and WELIN, S.: Über die Häufigkeit von Kolonpolypen bei ulzeröser Kolitis. Fortschr. Röntgenstr. 92 (1960), 567.

BACON, H. E.: Ulcerative colitis. J. B. Lippincott, Philadelphia 1958.

BARGEN, J. A. and COMFORT, M. W.: Association of chronic ulcerative colitis and multiple polyps. Ann. intern. Med. 4 (1930), 122.

BRANCH, B. D. and SLEDGE, C. B.: Inflammatory lesions of the colon simulating neoplasms. Gastroenterology 28 (1955), 981.

BUCKSTEIN, J.: The digestive tract in roentgenology. Vol. II, 2nd ed. J. B. Lippincott, Philadelphia 1953.

CATTELL, R. B.: Surgical treatment of ulcerative colitis. Gastroenterology 10 (1948), 63.

COUNSELL, P. B. and DUKES, C. E.: The association of chronic ulcerative colitis and carcinoma of the rectum and colon. Brit. J. Surg. 39 (1952), 485.

DICK, A. C., BERRIDGE, F. R. and GRAYSON, M. J.: The pathological basis of the radiological changes in ulcerative colitis. A study of cases treated by colectomy. Brit. J. Radiol. 32 (1959), 432.

FELDMAN, M.: Clinical roentgenology of the digestive tract. 4th ed. William & Wilkins, Baltimore 1957.

FELSEN, J. and WOLARSKY, W.: Chronic ulcerative colitis and carcinoma. Arch. int. Med. 84 (1949), 293.

HAWKES, S. Z. and SHIELDS, R. K.: Adenomatosis versus pseudopolyposis of large bowel. Bull. U. S. Army med. Dep. 6 (1946), 302.

JOHNSON, T. M. and ORR, T. G.: Carcinoma of colon secondary to chronic ulcerative colitis. Amer. J. dig. Dis. 15 (1948), 21.

KALIL, T. H. and ROBBINS, L. L.: Early roentgenologic changes in idiopathic ulcerative colitis. Radiology 53 (1949), 1.

LUMB, G., PROTHEROE, R. H. B. and RAMSAY, G. S.: Ulcerative colitis with dilatation of the colon. Brit. J. Surg. 43 (1955), 182.

Mc[illegible]T, H. A.: Ulcerative colitis. Amer. J. Proctol. 7 (1956), 402.
Pa[illegible]ORF, H.: Die Röntgendiagnostik der entzündlichen Dickdarmerkrankungen und ihre [illegible]grenzung gegenüber dem Carcinom. Röntgenpraxis 2 (1930), 732.
Po[illegible]L, M. H. and BERANBAUM, S. L.: The indenture sign in acute exudative colitis. Amer. [illegible]dig. Dis. 2 (1957), 382.
Rei[illegible]ERSCHEID, M.: Das Spätschicksal des Colitis ulcerosa-Kranken. Arch. klin. Chir. 293 [illegible]960), 558.
Ric[illegible]ITS, W. E., KIRSNER, J. B. and PALMER, W. L.: Chronic non-specific ulcerative colitis. [illegible]stroenterology 10 (1948), 1.
Rip[illegible]IN, C. B.: Perforation of colon in ulcerative colitis. Ann. Surg. 140 (1954), 872.
Ros[illegible]QVIST, H., LAGERCRANTZ, R., ÖHRLING, H. and EDLING, N.: Ulcerative colitis and [illegible]rcinoma coli. Lancet I (1959), 906.
Sla[illegible]Y, G. and BROOKE, B. N.: Cancer in ulcerative colitis. Lancet (1959: II), 694.
Spra[illegible]T, J. S., ACKERMAN, L. V. and MOYER, C. A.: Relationship of polyps of the colon to c[illegible]lonic cancer. Ann. Surg. 148 (1958), 682.
Stev[illegible]NSON, C. A. and WILSON, M.: Indications for the double contrast colon examination. [illegible]mer. J. Roentgenol. 71 (1954), 398.
Stierlin, E.: Die Radiographie in der Diagnostik der Ileozoekaltuberkulose und anderer Krankheiten des Dickdarms. Münch. med. Wschr. 58 (1911), 1231.
Welin, S.: Modern trends in diagnostic roentgenology of the colon. Brit. J. Radiol. 31 (1958), 453.

FROM THE DEPARTMENT OF RADIOLOGY, YALE UNIVERSITY MEDICAL SCHOOL, NEW HAVEN, U.S.A.

DEMONSTRATION OF BLOOD CURRENTS WITH RADIOPAQUE STREAMERS

by

T. DOBY and R. M. LOWMAN

As long as 450 years ago Leonardo da Vinci tried to see streamlines in his glass model of the heart. No one attempted to re-check his experiments until recent advances in radiology permitted us to show the flow and whirling of the blood in the heart chambers themselves.

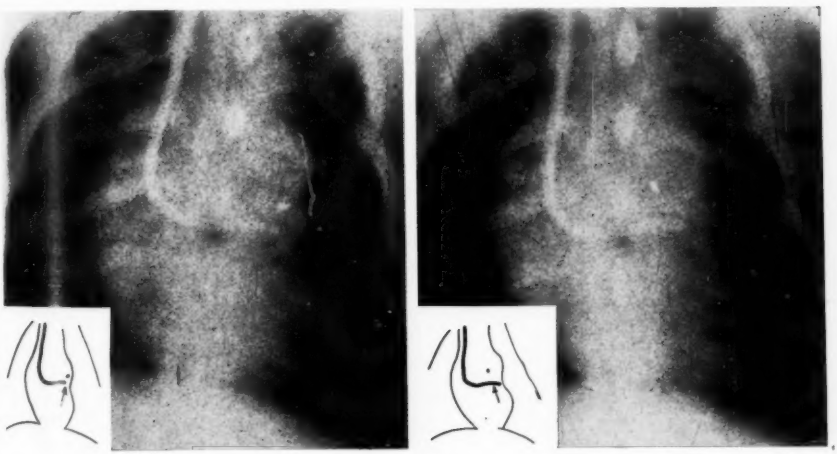
Some years ago when the finer details of angiocardiography were investigated more extensively, blood currents began to be demonstrated. The opaque jet through pulmonary valvular stenosis, ventricular septal defect and patent ductus arteriosus were recognized. Non-opaque jets shooting into already opacified compartments were also noted. The usual disadvantages encountered were the dimness of the jet outline and its rapid disappearance in the course of the angiographic procedure. A single film, or a few of the series only, showed the jet satisfactorily.

In vitro, or animal experiments, genuine, or radiopaque oil droplets can be followed (McDONALD et coll., DOTTER et coll. and STRAUFFER), by which the speed and direction of the currents may be demonstrated, but the observation is limited by the fairly rapid disappearance of the droplets from the area of study. The embolizing effect of the oil makes this kind of procedure impossible for humans.

The idea of observing blood currents by the use of radiopaque dots attached to easily movable threads, at the end of cardiac catheters, was suggested from the observation of windblown banners, or ribbons, at the top of masts of

This work was supported by a U. S. Public Health Service Grant No. H-4834 (Rad.).
Submitted for publication 21 November 1960.

Fig. 1. Cardiac catheter in the left main pulmonary artery with the streamer in the main branch supplying the lower lobe. (Slight left anterior oblique position.)



a b

Fig. 2. The tip of the catheter is in the outflow tract of the right ventricle. During systole the streamer is carried toward the orifice of the pulmonary artery. In diastole it falls back more medially.

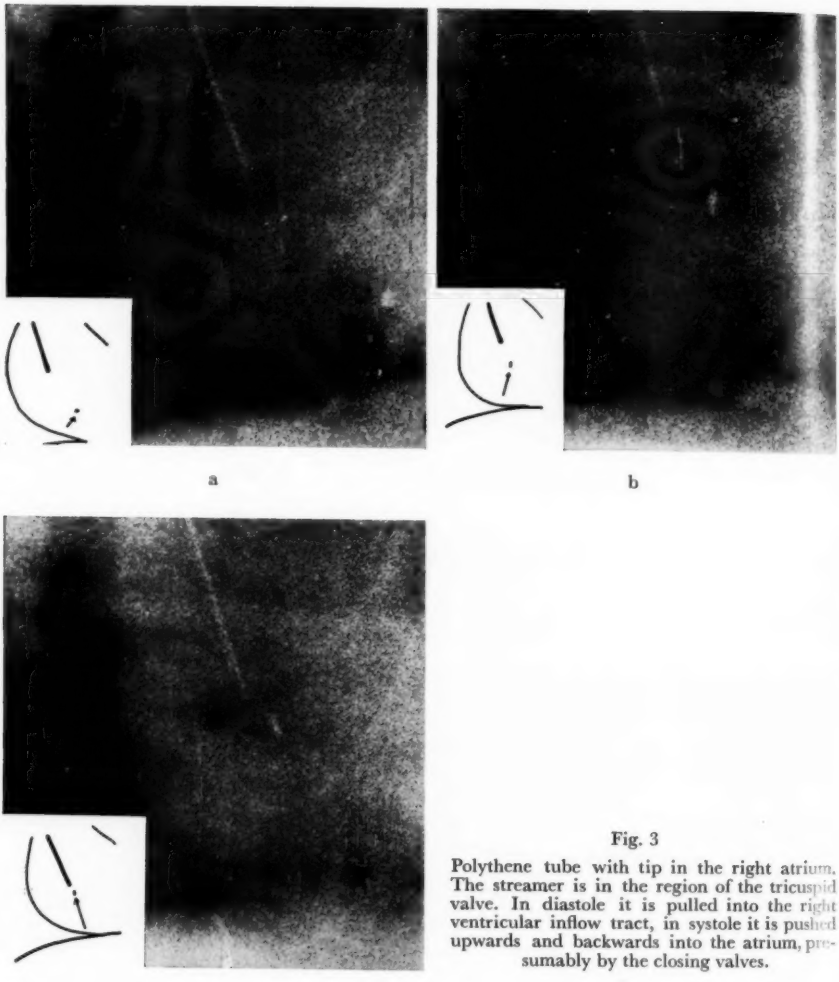


Fig. 3

Polythene tube with tip in the right atrium. The streamer is in the region of the tricuspid valve. In diastole it is pulled into the right ventricular inflow tract, in systole it is pushed upwards and backwards into the atrium, presumably by the closing valves.

yachts in a race. The catheters prepared for this purpose were led into the right ventricles of dogs. The procedure was filmed under fluoroscopic control with a 16 mm cine unit at 30 frames/sec through a 7 1/4″ Picker image amplifier.

Several kinds of radiopaque streamers were used. Those containing up to seven individual nylon threads with a radiopaque dot at one end of each tended to entangle in blood clots. Those containing only two threads kept apart

and moved individually. Most of the time, single threads were used. When the catheters were pushed as far as the main pulmonary artery, the blood current carried the streamers into secondary divisions, without allowing flapping in the narrow lumen of the artery.

When the catheters were pulled back, the streamers entered the ventricle and later the atrium where with more room they flapped around in the currents. Under the image amplifier they showed considerable whirling and were moved easily in all directions. No blood clots could be found at the dots after withdrawal of the catheters. Technical details of the preparation and handling of the radiopaque dots and catheters are published elsewhere (DOBY).

Whether the described principle can be utilized to diagnose shunts or back jets opposite normal flow, through insufficient valves in human subjects, will be decided by further examinations.

Acknowledgement

We wish to thank Dr H. J. Ricketts for his technical help and practical suggestions as surgeon in our experiments.

SUMMARY

'Radiopaque streamers' show the blood currents in cardiac chambers. The excursions caused by the flow of blood can be watched for a long time without danger to the experimental animal. Practical implications are suggested.

ZUSAMMENFASSUNG

‚Röntgendichte Wimpel' zeigen den Blutumlauf in den Herzkammer. Die durch den Blutstrom erzeugten Exkursionen können längere Zeit ohne Gefahr für das Versuchstier beobachtet werden. Praktische Anwendungsmöglichkeiten werden hervorgehoben.

RÉSUMÉ

Des banderoles radio-opaques mettent en évidence les courants sanguins dans les cavités cardiaques. On peut observer longuement, sans danger pour l'animal d'expérience, leurs mouvements dûs à l'écoulement du sang. Les auteurs examinent les conséquences pratiques de ces expériences.

REFERENCES

DA VINCI, LEONARDO: Quaderni d'anatomia, I—VI. C. L. Vangensten, A. Fonahn & H. Hopstock, Christiania 1911—1916.

DOBY, T.: Preparation of radiopaque streamers to show blood currents in heart chambers. (In press.)

DOTTER, C. T. and FRISCHE, L. H.: Radiologic technique for qualitative and quantitative study of blood flow. Circulation 18 (1958), 961.

MCDONALD, D. A. and POTTER, J. M.: Flow patterns in arteries recorded by high speed cinematography. J. Phys. 109 (1949) 17 P.

POTTER, J. M. and MCDONALD, D. A.: Cinematographic recording of the velocity of arterial blood flow. Nature 166 (1950), 596.

STAUFFER, H.: Lipiodol droplets followed in the blood vessels of experimental animals. Private communication 1960.

AUS DER ABTEILUNG FÜR RÖNTGENOLOGIE UND RADIOLOGIE (DIREKTOR: PROF. G. TENTSCHOV), DES INSTITUTS FÜR ÄRZTLICHE FACHSCHULUNG UND FORTBILDUNG, SOFIA, BULGARIEN.

HEPATOGRAPHIE MIT WASSERLÖSLICHEN KONTRASTMITTELN IM TIERVERSUCH

von

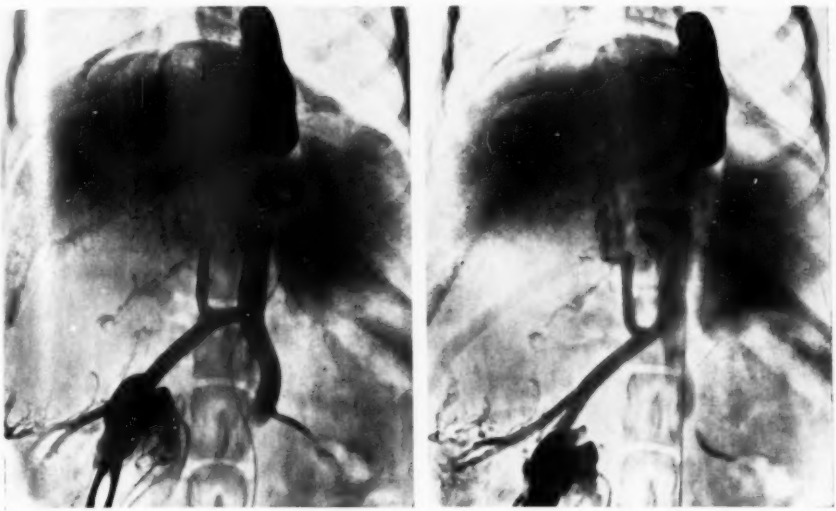
G. GOSPODINOW und L. WELITSCHKOW

Die Erkennung zystischer, primärer und metastatischer Neubildungen der Leber bereitet immer noch erhebliche Schwierigkeiten, wiewohl in den letzten Jahren einige neue Verfahren, darunter auch die lienoportale Venographie, eingeführt wurden.

Die vorliegende Mitteilung ist das Ergebnis unserer experimentellen Untersuchungen an 6 Hunden, wo wir versucht haben die Leber besser darzustellen und zu explorieren. Im Hinblick darauf, dass die Passage des Kontrastmittels bei der gewöhnlichen lienoportalen Venographie ziemlich schnell vor sich geht und also die Anfärbung des Lebers bei der Passage des Kontrastmittels durch das Kapillarnetz nur unbedeutlich dichter hervortritt, zielten wir in unseren Versuchen darauf ab, auf kurze Zeit die Passage des Kontrastmittels in der Kapillarphase aufzuhalten. Das liess sich durch eine auf mechanischem Wege erzeugte Stauung in den Lebervenen erreichen, und zwar durch Blockierung der unteren Hohlvene oberhalb der Einmündungsstelle der Lebervenen.

Methode. Für die Versuche dienten Hunde von 14 bis 20 kg Körpergewicht. Als Vorbereitung erhielten die Hunde 0,02 g Morphin je Kilogramm Körpergewicht, wodurch sie beruhigt werden und überdies (infolge des ausgelösten Erbrechens und der Defäkation) der Magen- und Darminhalt entleert wird,

Bei der Redaktion am 29. August 1960 eingegangen.



a b

Abb. 1. a) Am Schluss der Injektion von 20 ml Triopac 300. Einen Teil des Kontrastmittels ist im Kapillarnetz der Leber vorhanden. b) Zwei Minuten später. Ein beträchtlicher Teil des Kontrastmittels hat das Milz-Pfortader-System schon verlassen, doch sind immer noch einige der kleinen Pfortaderäste prall gefüllt.

so dass die Darstellung des Lebers erleichtert wird. Etwa 20 Minuten nach der Morphininjektion versetzte man die Hunde in tiefe Äthernarkose, die während der ganzen Versuchsdauer unterhalten wurde.

Ein zweikanaliger Katheter ‚Rüsch Super' Nr. 12 wurde in V. femoralis und durch der V. iliaca und der V. cava inferior bis zur Höhe der Zwerchfellgewölbe eingeführt. Wegen der Unmöglichkeit, die Milz beim Hunde perkutan zu punktieren, erreichte man sie durch Laparotomie. Mit einer Nadel von 0,8 mm Lumen in das Milzparenchym wurde ein hochkonzentriertes wasserlösliches Kontrastmittel (70 %ige Lösung von Diodon, Triopac 300, Triopac 400) in einer Menge von 1 ml/kg Körpergewicht eingeführt. Nach Einführung der Hälfte des Kontrastmittels (etwa 2 Sekunden nach Injektionsbeginn) füllte man durch den einen Katheterkanal den Gummiballon des Katheters gleichfalls mit Kontrastmittel, wodurch in den Lebervenen eine Stauung ausgelöst wurde. Das Kontrastmittel bleibt im Kapillarnetz der Leber gestaut und macht so alle ihre Abschnitte sichtbar.

Technik. Vor der Injektion des Kontrastmittels wird eine Übersichtsaufnahme der oberen Bauchhälfte gemacht. Am Schluss der Injektion macht

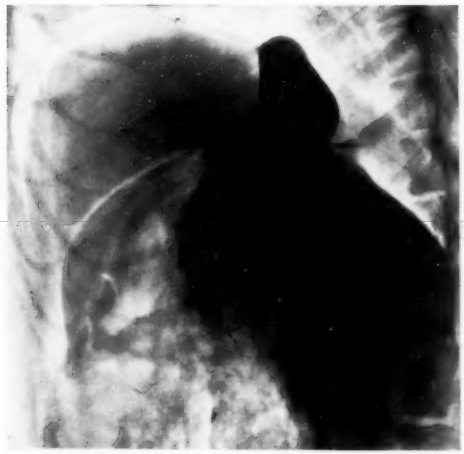


Abb. 2. Aufnahme in der 6. Minute vom Injektionsschluss, linker Seitenlage. Die Grenzen der ganzen Leber und einiger der Leberteile sind klar umrissen.

man eine Aufnahme in Rückenlage. Darauf sieht man sehr gut gefüllt V. lienalis, die V. portae und deren Verästelungen. Einen Teil des Kontrastmittels erblickt man auch im Kapillarnetz der Leber (Abb. 1a). Zwei Minuten nach der Injektion hat man eine starke Kontrastmittelspeicherung der Leber (Abb. 1b). Man sieht dass ein beträchtlicher Teil des Kontrastmittels das Milz-Pfortader-System schon verlassen hat; doch sind immer noch einige der kleinen Pfortaderäste prall gefüllt. In der 4. bzw 6. Minute vom Injektionsschluss macht man Aufnahmen in rechter bzw linker Seitenlage. Darauf sieht man die Grenzen der ganzen Leber und auch einiger der Leberteile klar umrissen (Abb. 2). In einigen Fällen wurde Tomographie versucht — 4 Schnitte über je 2 cm auf der Höhe der Leber. Auf solchen Bildern treten die Lebergrenzen deutlich hervor. Die Stauung in den Lebervenen hielt etwa 6 Minuten an und wurde nach der letzten Aufnahme behoben. Während der Untersuchung spritzte man einigemal eine Lösung zitronensauren Natriums durch den einen der Katheterkanäle zwecks Vorbeugung von Gerinnselbildung ein.

Um das Verfahren auf seine Harmlosigkeit zu prüfen, tötete man die Hunde mit schwefelsaurem Magnesium (intrakardial) in verschiedenen Abständen vom Tage der Untersuchung, zwischen dem 3. und 45. Tage. Ausser der makroskopischen Untersuchung der Milz, Leber, der Nieren der unteren Hohlvene, der Pfortader und der V. lienalis, machte man auch eine

histologische Untersuchung verschiedener Abschnitte derselben (Dr Doitschinov), ohne irgendwelche Befunde einer Schädigung.

Man wählte den Einführungsweg des Kontrastmittels durch eine Milzpunktion im Hinblick auf die Möglichkeit, bei einer Anwendung des Verfahrens am Menschen, die Milz perkutan zu punktieren.

ZUSAMMENFASSUNG

Eine Methode für Hepatographie wird beschrieben, die eine beträchtliche Verbesserung der Abbildung des Milz-Pfortader-Systems erzielt. Durch Verzögerung der Kontrastmittelpassage wird die Leber sehr deutlich sichtbar und die Kontrastmittelspeicherung ist intensiv genug um Kontrastdefekte auseinanderzuhalten, deren Substrat zystische, primärneoplastische oder metastatische Neubildungen sind.

SUMMARY

A method of hepatography which produces considerable improvement in the demonstration of the lienoportal system is described. The slowness of the passage of the contrast medium ensures good filling of the liver and the degree of opacity obtained is such that contrast defects due to cysts, primary growths, or metastatic deposits may be differentiated.

RÉSUMÉ

Les auteurs décrivent une méthode d'hépatographie qui améliore considérablement la mise en évidence du système spléno-portal. La lenteur du passage du moyen de contraste assure une bonne imprégnation hépatique et le degré d'opacité obtenu est tel qu'il permet de distinguer les défauts de contraste dus à des kystes, à des tumeurs primitives ou à des métastases.

SCHRIFTTUM

Abeatici, S. et Campi, L.: Sur les possibilités de l'angiographie hépatique. La visualisation du système portal. Acta radiol. 36 (1951), 383.

Child, Ch., O'Sullivan, W., Payne, M. and McClure, R.: Portal venography. Radiology 57 (1951), 691.

Csakany, G. und Tardos, Z.: Splenoporto-Hepatographie. Tierversuche. Fortschr. Röntgenstr. 92 (1960), 410.

Moore, G. and Brindenbaugh, R.: Roentgen demonstration of the venous circulation in the liver: portal venography. Radiology 57 (1951), 685.

Rappaport, A. M.: Hepatic venography. Acta radiol. 36 (1951), 165.

Rigler, L., Olfeld, P. and Krumbach, R.: Roentgen hepatography by injection of a contrast medium into the aorta. Radiology 60 (1953), 363.

Shishkin, V. P.: Splenoportographia. (In Russian.) Vestn. Rentgenol. Radiol. 5 (1955), 79. — Krakowski, N. I. und Zodiev, V. V.: Über die Methodik der Splenoportographie und ihre diagnostische Bedeutung, Vestn. Rentgenol. Radiol. 21 (1956), 54 (r).

Statten, Sture: Percutaneous lieno-portal venography in the demonstration of liver masses. Acta radiol. 52 (1959), 353.

Thomas, Sidney F., Henry, George W. and Kaplan, Henry S.: Hepatolienography: Past, present and future. Radiology 57 (1951), 669.

Tori, G.: Hepatic venography in man. Acta radiol. 39 (1953), 89.

WANNAGAT, L.: Bedeutet die laparoskopische Splenoportographie einen Fortschri auf dem Gebiete der medizinischen Röntgendiagnostik? Fortschr. Röntgenstr. 84 (56), 509.

ZEGER, Z., ALBOT, G. et ARVAY, N.: La phlébographie portale dans l'exploration des ffec-tions hépatospléniques. Presse méd. 59 (1951), 1230.

ZODIEV, V. V., SILAGIN, P. V. und EVSTATNEEVA, XX.: Das Verfahren der Portovenog phie und seine diagnostische Bedeutung. Vestn. Rentgenol. Radiol. 2 (1955), 58.

FRO THE RADIOISOTOPE RESEARCH LABORATORY (DIRECTOR: PROF. G. NYLIN)
AND THE HEART CLINIC (DIRECTOR: DOCENT S. ÅKESSON), SÖDERSJUKHUSET, STOCKHOLM, SWEDEN.

CEREBRAL CIRCULATION STUDIED WITH LABELLED RED CELLS IN HEALTHY MALES

by

GUSTAV NYLIN, SVEN HEDLUND and OLOF REGNSTRÖM

Serial angiography has been used for the determination of the cerebral circulation time. The results obtained depend on the technique employed and have sometimes varied considerably (MONIZ 1932, SCHURR & WICKBOM 1952, GREITZ 1956, TÖNNIS & SCHIEFER 1959, and others). It has been shown that the speed of the cerebral circulation differs in the arterial and venous phases and that marked changes occur in pathologic cases.

The cerebral blood flow has been studied previously by NYLIN et coll. (1955, 1958 and 1960) and some recent work is in the press. In the present paper some further information on the results obtained in studies of the cerebral blood flow, blood volume and circulation time in healthy males is given, and the dilution curves forming the basis of the calculations are presented in a series of diagrams.

Material and Method. Thirty-four healthy males, all volunteers, aged between 26 and 53 years (mean 36 years) were studied. They were carefully examined prior to the circulatory studies: the histories, state of the general and neurologic systems, as well as the heart volume determinations and ECG being all recorded. No abnormality was found.

Following an injection of a small dose of morphine-scopolamine, the subject was placed in the recumbent position. The two internal jugular bulbs and the internal carotid arteries

Submitted for publication 10 November 1960.

were punctured percutaneously and a first intravenous injection of 1.5 ml of the subject's own labelled blood, with simultaneous sampling at one-second intervals from the two jugular bulbs and one carotid artery, were performed. Injections of the same amount of blood into two carotid arteries, one after the other, were then made and samples from the bulbs were withdrawn after each injection. The techniques used have been previously described (NYLIN et coll. 1958, 1960).

The blood pressure and pulse rate were continuously recorded before and during the examination. It was noted that these were within the limits of the normal values under basal conditions. No obvious discomfort or complications were observed in any of the cases examined.

The calculation of the cerebral blood flow was based on the four dilution curves obtained from the jugular bulbs after the two injections into the internal carotid arteries. The mathematical derivation of the equations has been given in a paper by ANDERSSON (1957) and NYLIN et coll. (1960). It is important that the injections be performed sufficiently high up in the internal carotid artery to avoid regurgitation into the external carotid artery. In a few cases, however, slight regurgitation cannot be excluded with certainty and may have caused an error in the calculation of the cerebral blood flow. If the sum of the activity of the two ipsilateral peaks in pro mille of injected activity is high or above 30 to 40, it is very probable that most or all the activity has reached the brain, as indicated in our earlier publications. The product of the cerebral blood flow and the mean circulation time represents the cerebral blood volume. The mean circulation time has been calculated from the results obtained during the intravenous injection.

The circulation times through the brain were determined from the dilution curves obtained from the jugular bulbs after the two carotid injections. The values are represented by the appearance time (App.), the peak concentration time (Peak), and the disappearance time (Disapp.) for ipsilateral and contralateral dilution curves. The disappearance time is defined as the time when the down slope of the curve reaches a constant level.

Results

The dilution curves obtained are recorded in Figs 1 to 25. Some of the studies are incomplete due to difficulties in puncturing both the internal carotid arteries on the same occasion. The age of the subjects may be found from data recorded in the diagrams.

The contralateral bulb generally drains less activity than the ipsilateral one, as shown in the figures. Not infrequently however, the injected erythrocytes are drained symmetrically through the two bulbs after one carotid injection. This occurred in 10 cases in the present material; in 8 cases either no or only very slight activity was drained from the contralateral bulb after one intracarotid injection and in 2 cases the injection was made into the external carotid artery and no activity at all passed via the brain into the jugular bulbs (Figs 15 and 23).

When the flow through the right and the left jugular bulb is calculated separately, the right bulb drains more of the cerebral blood flow than the left bulb, i. e. on an average 62 % of the cerebral blood flow passes through the right bulb and 38 % through the left bulb.

The asymmetrical drainage of the labelled cells through the jugular bulbs

may depend partly upon the anatomy of the cerebral veins, but also upon the flow being laminar in the sagittal sinus, which we presume prevents the complete mixing of the blood from the two hemispheres. This opinion is supported by the investigations of HELPS and MCDONALD (1954) and NYLIN et coll. (1960).

The dilution curves obtained for the two bulbs are as a rule identical after the intravenous injection when all arteries to the brain are provided with labelled red cells. In 8 cases or 28 % of the present material, slightly asymmetrical curves from the two bulbs were obtained; in only one case (Fig. 9) was the asymmetry marked. In clinical cases, such as those of cerebral atherosclerosis, nonsymmetrical curves are mostly found; this will be dealt with in another paper.

The values of the cerebral blood flow varied from 667 ml to 1 238 ml, with a mean of 915 ml in the present material; the mean is 11.9 per cent of the cardiac output, which was determined as averaging 7 900 ml. No correlation was observed between the cardiac output and the cerebral blood flow, nor was any correlation found between the cerebral blood flow and the age of the subjects in the present series.

The cerebral blood volume varied from 87 ml to 183 ml, with a mean of 132 ml, this being 2.7 per cent of the total blood volume of the body. The mean of the total blood volume was 5 230 ml.

The circulation times based on the dilution curves from the two internal jugular veins after the injections into both the carotid arteries are shown in the Table on next page. There were only slight variations in the determined values. The appearance time and peak concentration times were shorter from the ipsilateral bulb than from the contralateral bulb but the values for the disappearance time were about the same. For the parameters mentioned, the same values were found for both the ipsilateral and the contralateral bulb, irrespective of whether the labelled cells were injected into the right or the left carotid artery. The appearance time varied in general from 2 to 4 sec for the ipsilateral and from 3 to 5 sec for the contralateral bulb, the peak concentration time varying from 5 to 7 sec for the ipsilateral and from 6 to 8 sec for the contralateral bulb. The disappearance time was generally from 12 to 16 sec for both bulbs. There were only two exceptions for rather high values (Figs 6 and 12). No correlation was found to exist between these parameters of circulation time and age. In our material of old people up to 80 years of age we have observed perfectly normal and short circulation times, for example in a 77-year-old woman with slight hypertension (Fig. 2).

The mean circulation time calculated from the intravenous injection was found to be 8.5 sec with an average range of from 7 to 10 sec. There was no correlation between the mean circulation time and the cerebral blood flow in the present series of normal males.

Table

The cerebral circulation times in seconds in healthy males (from carotid artery to jugular bul

		App.	Peak	Disap
Injection into right carotid artery				
Ipsilateral bulb	(mean value)	3.2	6.2	14.2
	(number of cases)	(27)	(27)	(27)
	(range)	2—5	4—10	12—2
Contralateral bulb	(mean value)	4.5	7.1	13.1
	(number of cases)	(24)	(24)	(24)
	(range)	3—6	6—9	9—18
Injection into left carotid artery				
Ipsilateral bulb	(mean value)	3.1	6.1	14.9
	(number of cases)	(24)	(24)	(24)
	(range)	2—4	4—8	12—21
Contralateral bulb	(mean value)	4.0	6.7	13.9
	(number of cases)	(25)	(25)	(25)
	(range)	2—6	5—8	11—16

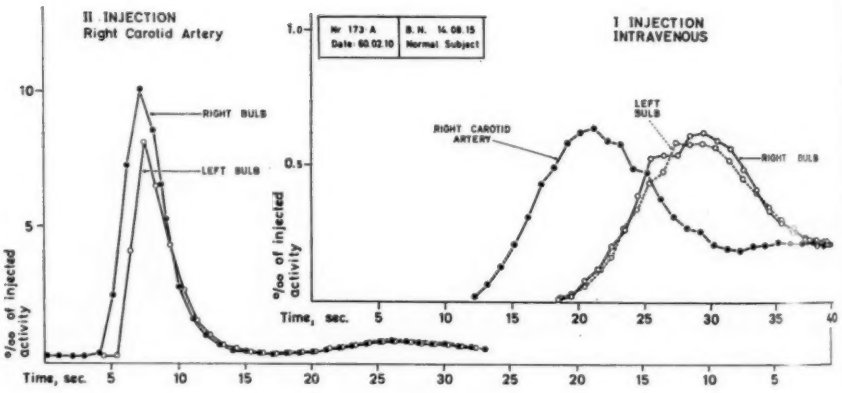


Fig. 1

Right car. art.:	Ipsilat. bulb	Contralat. bulb
App.	5 sec	6 sec
Peak	7 »	7 »
Disapp.	14 »	14 »

Cardiac output 7 000 ml in
Mean circulation time 7.1 sec
Total blood volume 5 59 ml
Heart volume 810 ml: 3 ml/m²

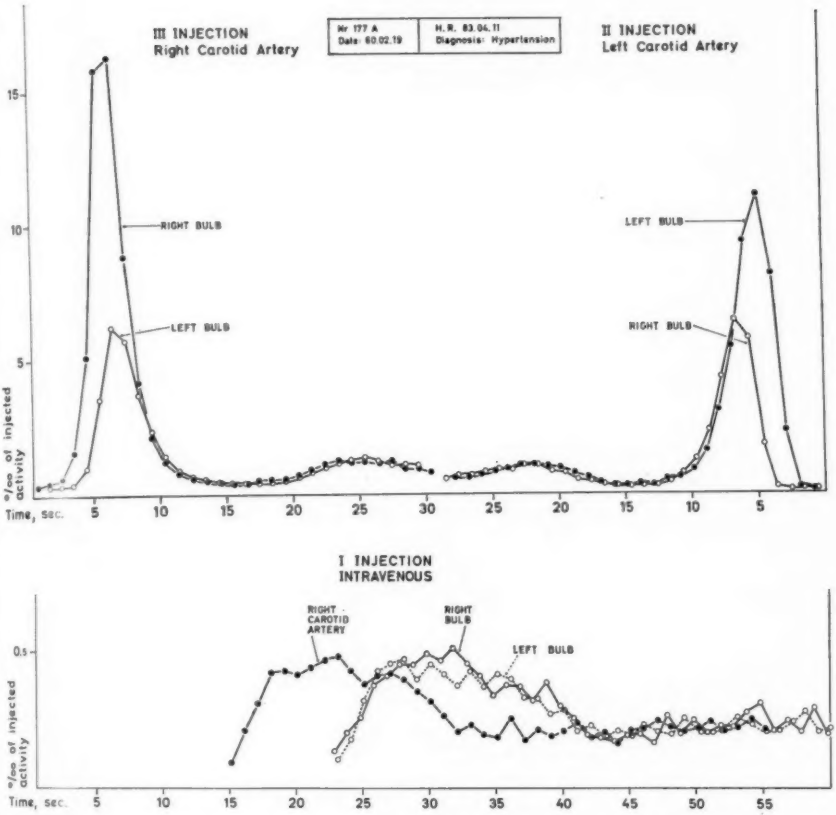


Fig. 2 77 years

Right car. art.:	Ipsilat. bulb	Contralat. bulb	Left car. art.:	Ipsilat. bulb	Contralat. bulb
App.	4 sec	5 sec	App.	3 sec	4 sec
Peak	6 »	7 »	Peak	5 »	7 »
Disapp.	13 »	13 »	Disapp.	13 »	13 »

Cardiac output 6 500 ml/min
Mean circulation time 9.1 sec

Total blood volume 4 191 ml
Heart volume 670 ml: 410 ml/m²

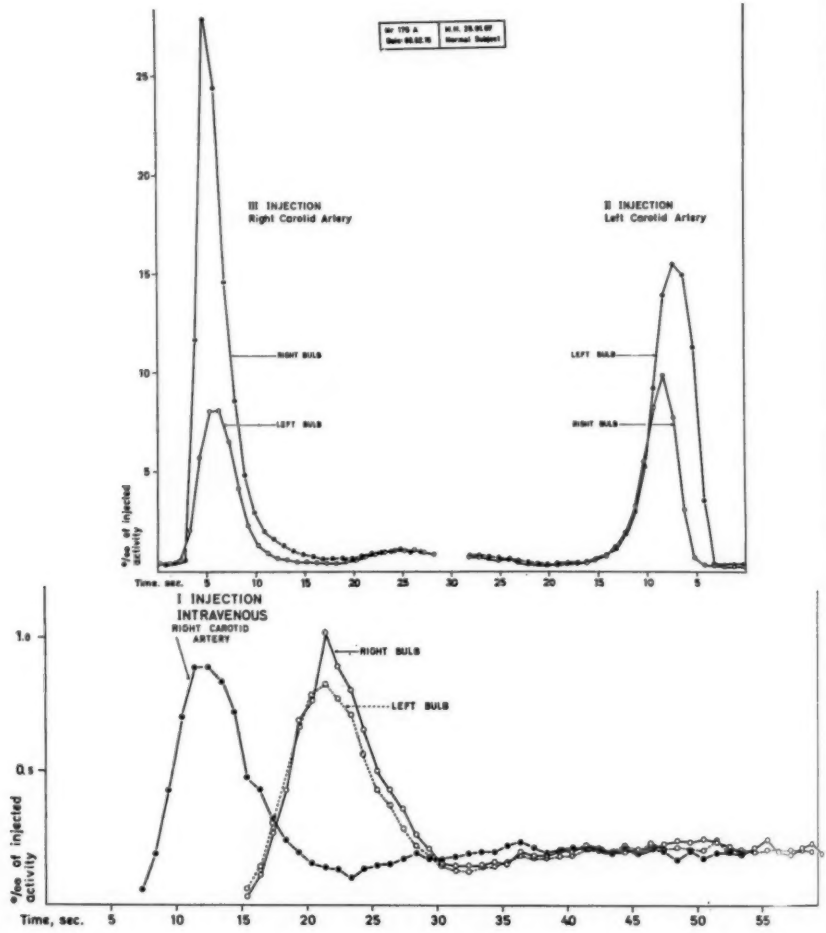


Fig. 3

35 years

Right car. art.:	Ipsilat. bulb	Contralat. bulb	Left car. art.:	Ipsilat. bulb	Contralat. bulb
App.	3 sec	3 sec	App.	4 sec	5 sec
Peak	5 »	6 »	Peak	7 »	8 »
Disapp.	15 »	13 »	Disapp.	15 »	15 »

Cerebral blood flow 824 ml/min (10.2 % of cardiac output)
Cerebral pool volume 130 ml (2.4 % of total blood volume)
Cardiac output 8 100 ml/min — Total blood volume 5 334 ml
Mean circulation time 9.5 sec — Heart volume 720 ml: 380 ml/m²

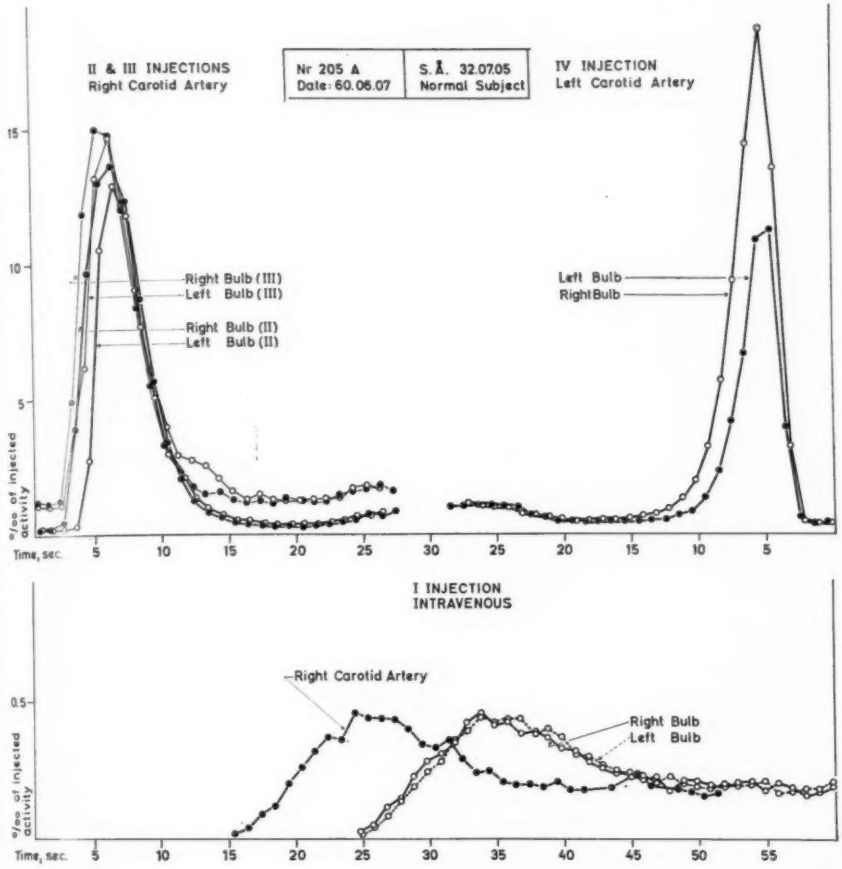


Fig. 4 28 years

Right car. art.:	Ipsilat. bulb	Contralat. bulb	Left car. art.:	Ipsilat. bulb	Contralat. bulb
App.	3 sec	3 sec	App.	3 sec	3 sec
Peak	6 »	7 »	Peak	5 »	5 »
Disapp.	15 »	15 »	Disapp.	13 »	12 »

Cerebral blood flow 943 ml/min (12.5 % of cardiac output)
Cerebral pool volume 155 ml (2.6 % of total blood volume)
Cardiac output 7 500 ml/min — Mean circulation time 9.9 sec
Total blood volume 6 045 ml — Heart volume 670 ml : 350 ml/m²

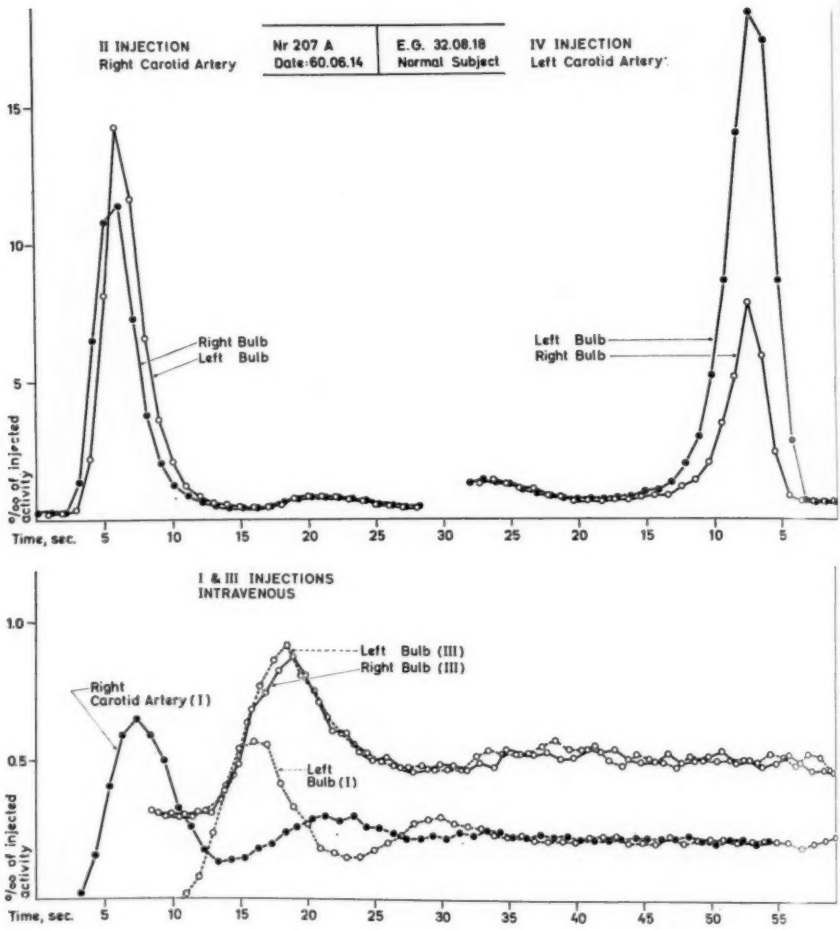


Fig. 5

20 years

Right car. art.:	Ipsilat. bulb	Contralat. bulb	Left car. art.:	Ipsilat. bulb	Contralat. bulb
App.	3 sec	4 sec	App.	3 sec	4 sec
Peak	6 »	6 »	Peak	7 »	7
Disapp.	13 »	14 »	Disapp.	16 »	14

Cerebral blood flow 1 219 ml/min — Cerebral pool volume 159 ml (3.3 % of total blood volume)
Mean circulation time 7.8 sec — Total blood volume 4 859 ml — Heart volume 640 ml : 360 ml/m²

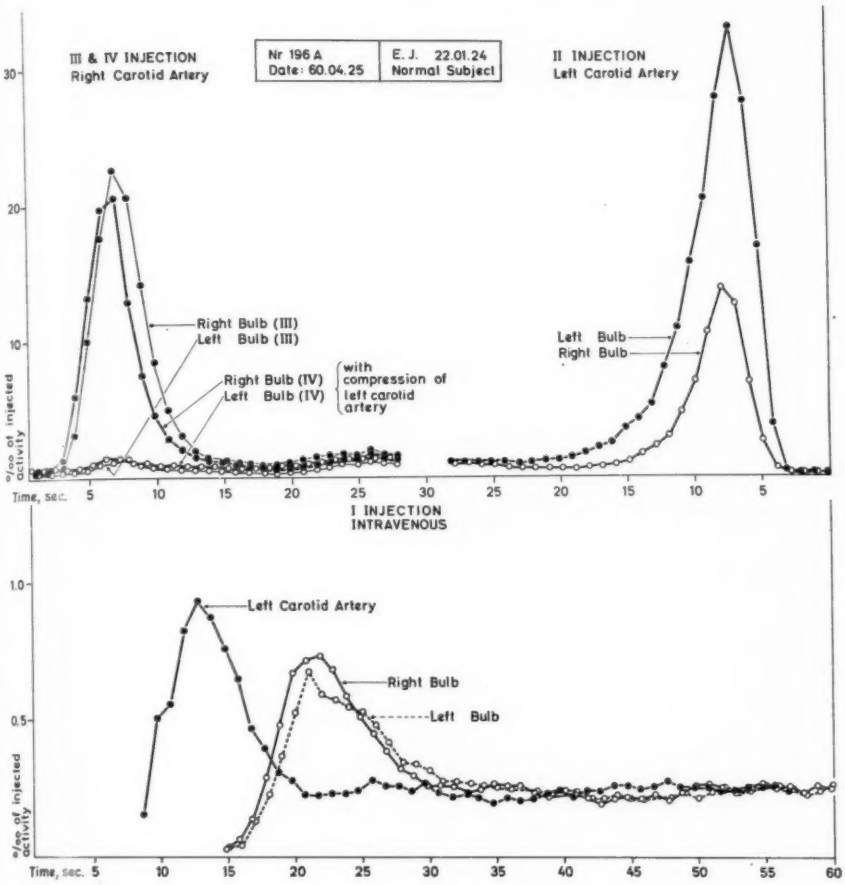


Fig. 6 38 years

Right car. art.:	Ipsilat. bulb	Contralat. bulb	Left car. art.:	Ipsilat. bulb	Contralat. bulb
App.	3 sec	5 sec	App.	4 sec	5 sec
Peak	6 »	7 »	Peak	7 »	8 »
Disapp.	13 »	10 »	Disapp.	18 »	15 »

Cerebral blood flow 667 ml/min (8.8 % of cardiac output)
Cerebral pool volume 116 ml (2.8 % of total blood volume)
Cardiac output 7 600 ml/min — Total blood volume 4 151 ml
Mean circulation time 10.4 sec — Heart volume 610 ml : 330 ml/m²

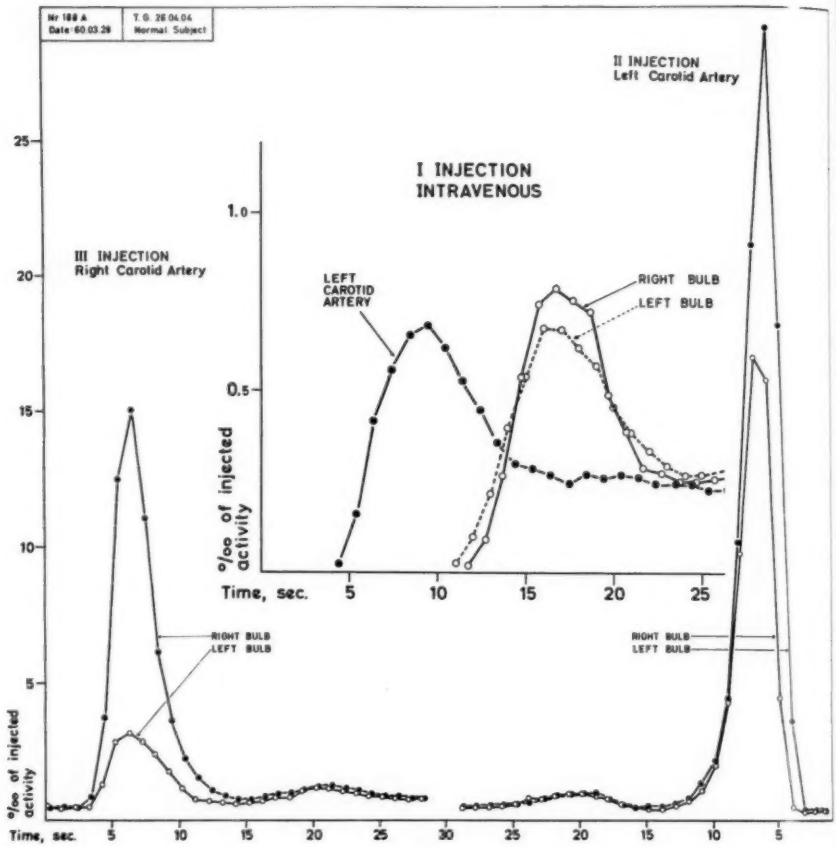


Fig. 7

34 years

Right car. art.:	Ipsilat. bulb	Contralat. bulb	Left car. art.:	Ipsilat. bulb	Contralat. bulb
App.	3 sec	4 sec	App.	3 sec	4 sec
Peak	6 »	6 »	Peak	6 »	7 »
Disapp.	13 »	12 »	Disapp.	13 »	13 »

Cerebral blood flow 1 077 ml/min (11.4 % of cardiac output)
Cerebral pool volume 126 ml (2.9 % of total blood volume)
Cardiac output 9 400 ml/min — Mean circulation time 7.0 sec
Total blood volume 4 320 ml — Heart volume 600 ml : 340 ml/m²

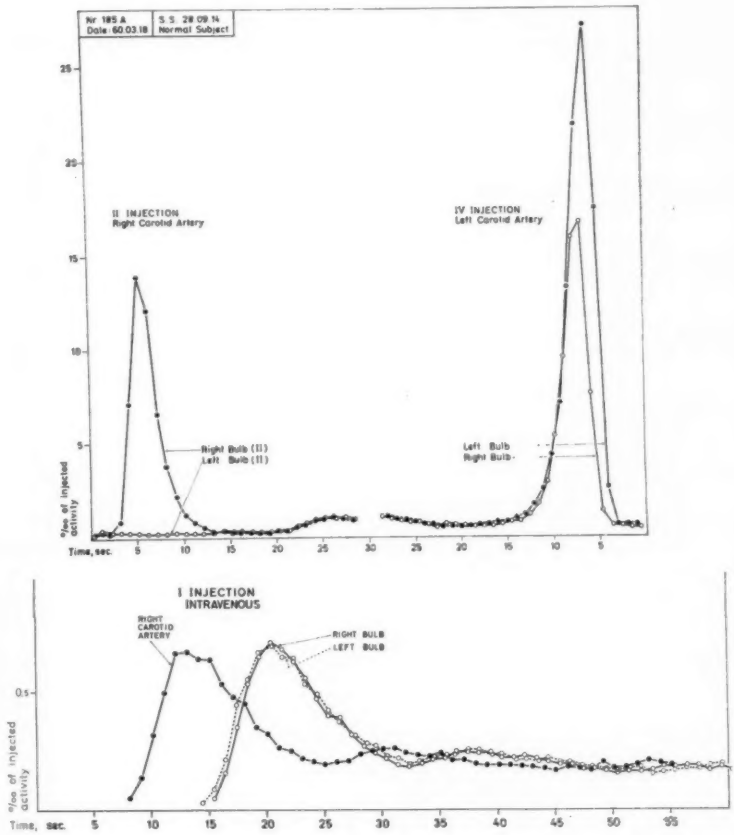


Fig. 8

32 years

Right car. art.:	Ipsilat. bulb	Contralat. bulb	Left car. art.:	Ipsilat. bulb	Contralat. bulb
App.	3 sec	0 sec	App.	4 sec	5 sec
Peak	5 »	0 »	Peak	6 »	6 »
Disapp.	12 »	0 »	Disapp.	14 »	14 »

Cerebral blood flow 948 ml/min (12.5 % of cardiac output)
Cerebral pool volume 120 ml (2.1 % of total blood volume)
Cardiac output 7 600 ml/min — Total blood volume 5 621 ml
Mean circulation time 7.6 sec — Heart volume 780 ml : 420 ml/m²

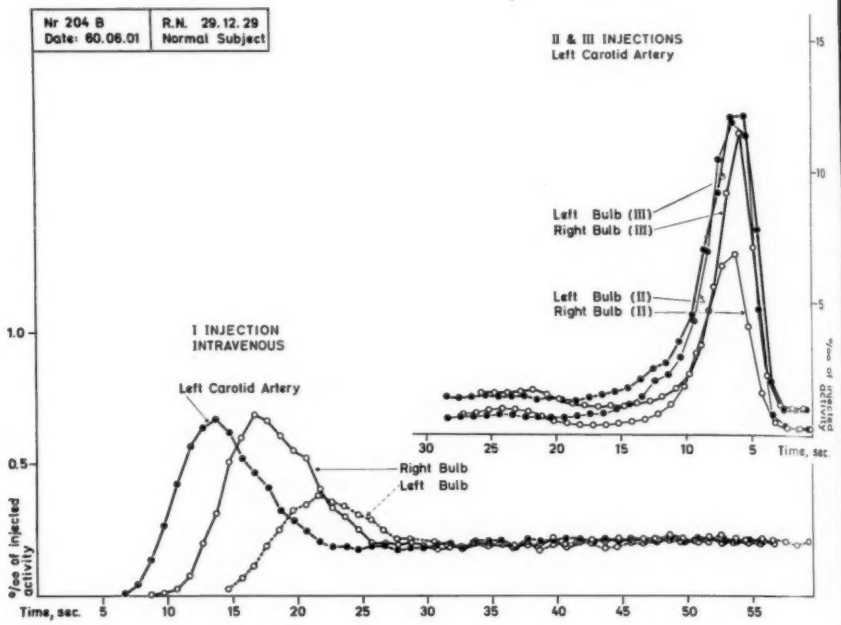


Fig. 9

31 years

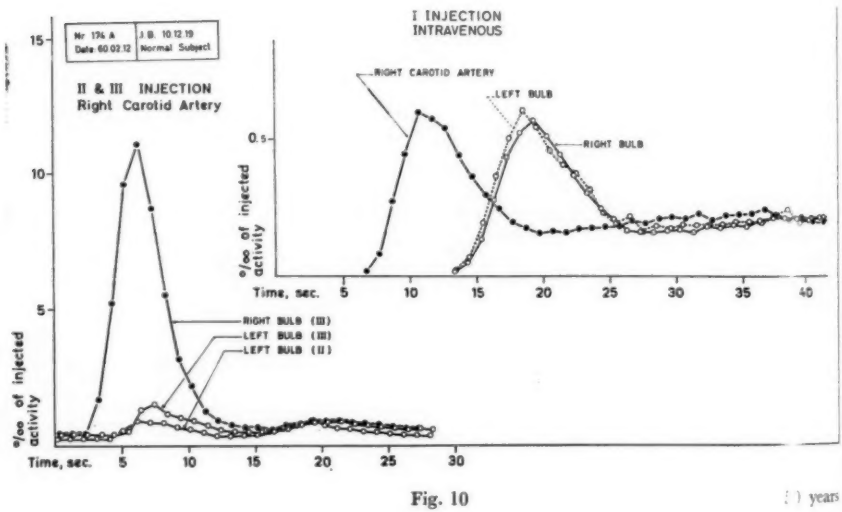


Fig. 10

) years

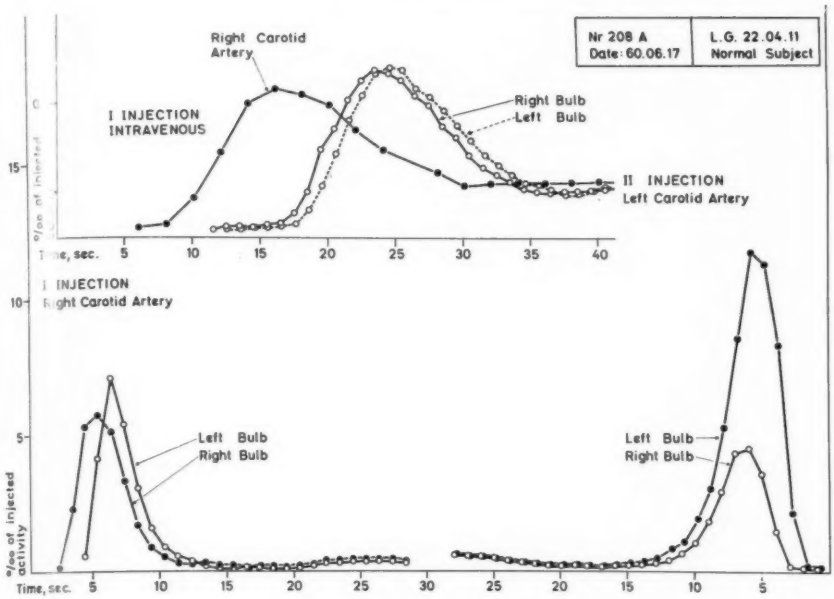


Fig. 11 38 years

Right car. art.:	Ipsilat. bulb	Contralat. bulb	Left car. art.:	Ipsilat. bulb	Contralat. bulb
App.	3 sec	4 sec	App.	2 sec	3 sec
Peak	6 »	7 »	Peak	6 »	6 »
Disapp.	12 »	14 »	Disapp.	15 »	14 »

Cardiac output 7 100 ml/min
Total blood volume 8 716 ml

Mean circulation time 6.1 sec
Heart volume 800 ml : 410 ml/m²

Legend for Fig. 9 (opposite page)

Left car. art.:	Ipsilat. bulb	Contralat. bulb
App.	3 sec	4 sec
Peak	6 »	6 »
Disapp.	16 »	13 »

Cerebral blood flow 1 238 ml/min (15.2 % of cardiac output)
Cerebral pool volume 165 ml (3.2 % of total blood volume)
Cardiac output 8 200 ml/min — Total blood volume 5 233 ml
Mean circulation time 8.0 sec — Heart volume 620 ml : 320 ml/m²

Legend for Fig. 10 (opposite page)

Right car. art.:	Ipsilat. bulb	Contralat. bulb
App.	3 sec	5 sec
Peak	6 »	7 »
Disapp.	13 »	12 »

Cardiac output 11 700 ml/min
Mean circulation time 7.6 sec
Total blood volume 5 394 ml
Heart volume 770 ml : 400 ml/m²

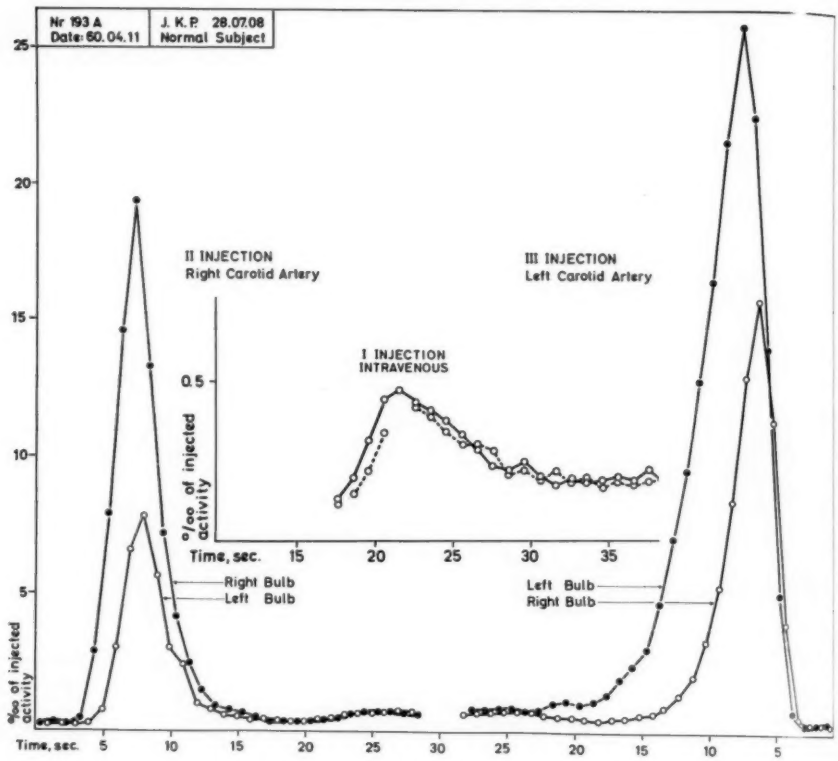


Fig. 12

32 years

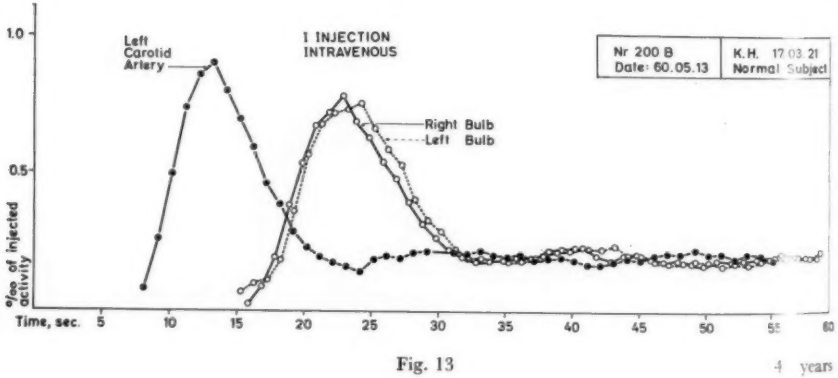


Fig. 13

4 years

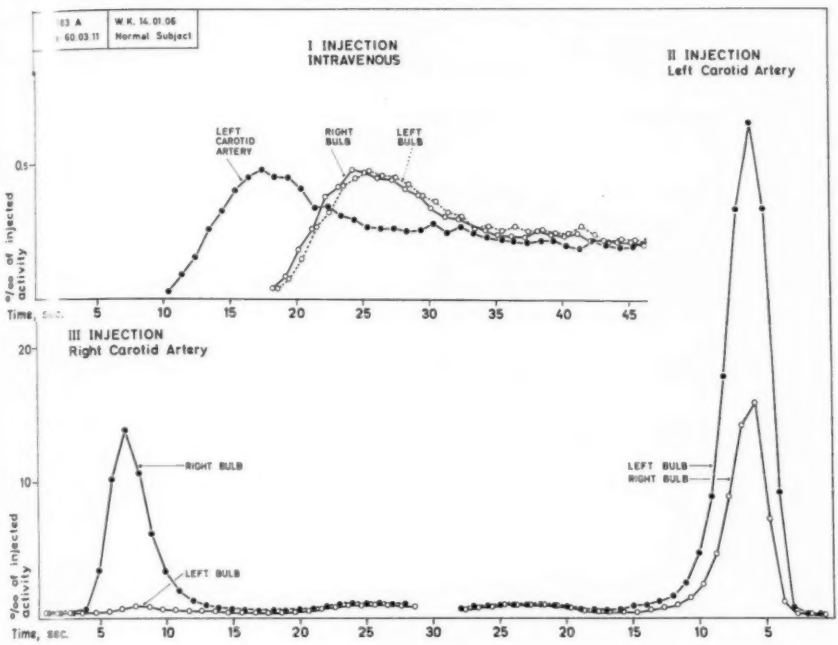


Fig. 14 46 years

Right car. art.:	Ipsilat. bulb	Contralat. bulb	Left car. art.:	Ipsilat. bulb	Contralat. bulb
App.	4 sec	6 sec	App.	3 sec	4 sec
Peak	7 »	8 »	Peak	6 »	6 »
Disapp.	14 »	12 »	Disapp.	16 »	16 »

Cerebral blood flow 1 115 ml/min (15.1 % of cardiac output)
Cerebral pool volume 167 ml (3.2 % of total blood volume)
Cardiac output 7 400 ml/min — Total blood volume 5 197 ml
Mean circulation time 9.0 sec — Heart volume 820 ml : 390 ml/m²

Legend for Fig. 12 (opposite page)

Right car. art.:	Ipsilat. bulb	Contralat. bulb	Left car. art.:	Ipsilat. bulb	Contralat. bulb
App.	3 sec	5 sec	App.	3 sec	4 sec
Peak	7 »	8 »	Peak	8 »	6 »
Disapp.	16 »	15 »	Disapp.	21 »	15 »

Cerebral blood flow 833 ml/min (7.4 % of cardiac output)
Cardiac output 11 000 ml/min — Total blood volume 5 583 ml — Heart volume 790 ml : 380 ml/m²

Legend for Fig. 13 (opposite page)

Left car. art.:	Ipsilat. bulb	Contralat. bulb
App.	3 sec	5 sec
Peak	5 »	7 »
Disapp.	13 »	12 »

Cardiac output 7 400 ml/min
Mean circulation time 10.8 sec
Total blood volume 5 090 ml
Heart volume 940 ml : 570 ml/m²

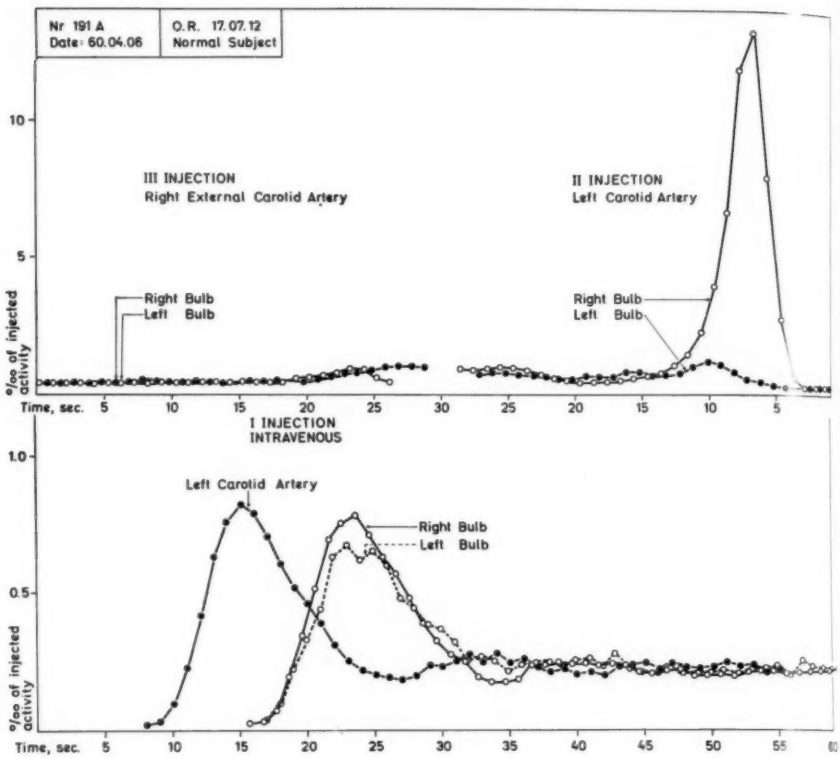


Fig. 15 43 years

Left car. art.:	Ipsilat. bulb	Contralat. bulb	Mean circulation time 9.1 sec
App.	0 sec	4 sec	Total blood volume 5 114 ml
Peak	0 »	7 »	Heart volume 780 ml : 425 ml/m²
Disapp.	0 »	16 »	

Legend for Fig. 16 (opposite page)

Right car. art.:	Ipsilat. bulb	Contralat. bulb	Left car. art.:	Ipsilat. bulb	Contralat. bulb
App.	3 sec	3 sec	App.	2 sec	2 sec
Peak	4 »	6 »	Peak	5 »	5 »
Disapp.	13 »	13 »	Disapp.	12 »	11 »

Cerebral blood flow 1 067 ml/min (11.5 % of cardiac output)
Cerebral pool volume 130 ml (2.4 % of total blood volume)
Cardiac output 9 300 ml/min — Total blood volume 5 337 ml
Mean circulation time 7.3 sec — Heart volume 725 ml : 370 ml/m²

Legend for Fig. 17 (opposite page)

Right car. art.:	Ipsilat. bulb	Contralat. bulb	Cardiac output 8 000 ml/min
App.	3 sec	4 sec	Mean circulation time 6.8 sec
Peak	6 »	6 »	Total blood volume 4 878 ml
Disapp.	13 »	9 »	Heart volume 810 ml: 450 ml/m²

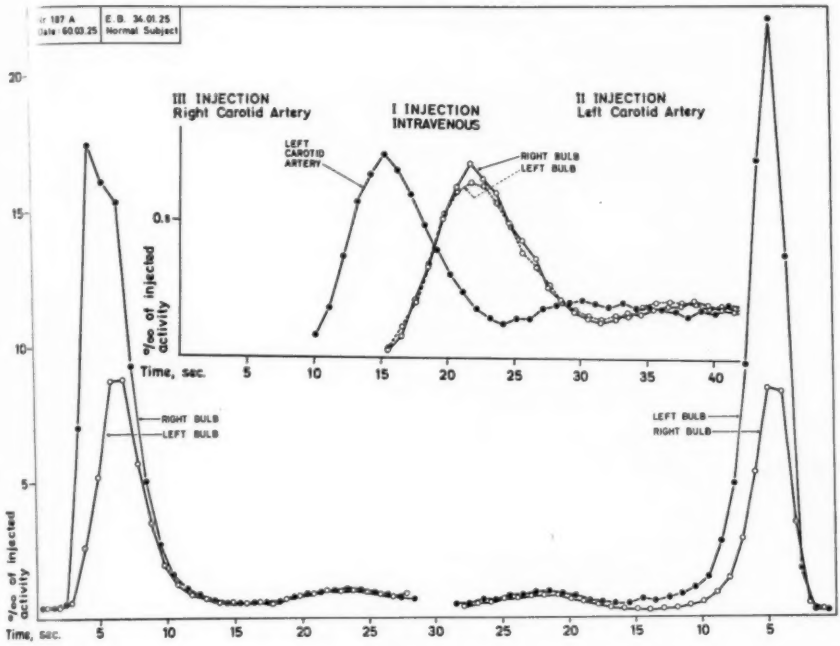


Fig. 16 26 years

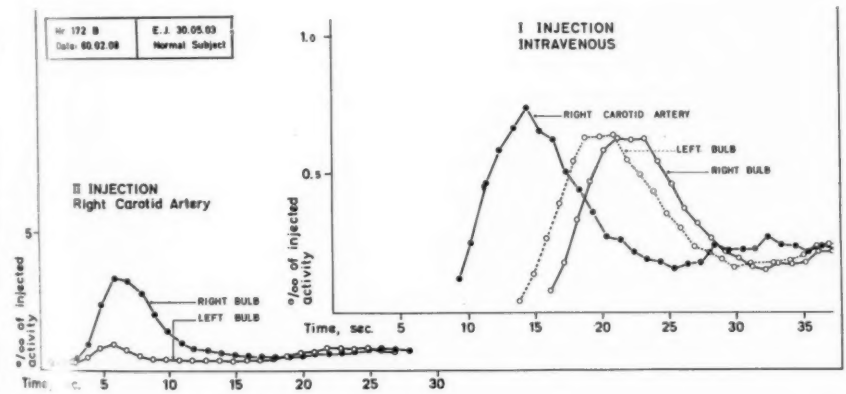


Fig. 17 30 years

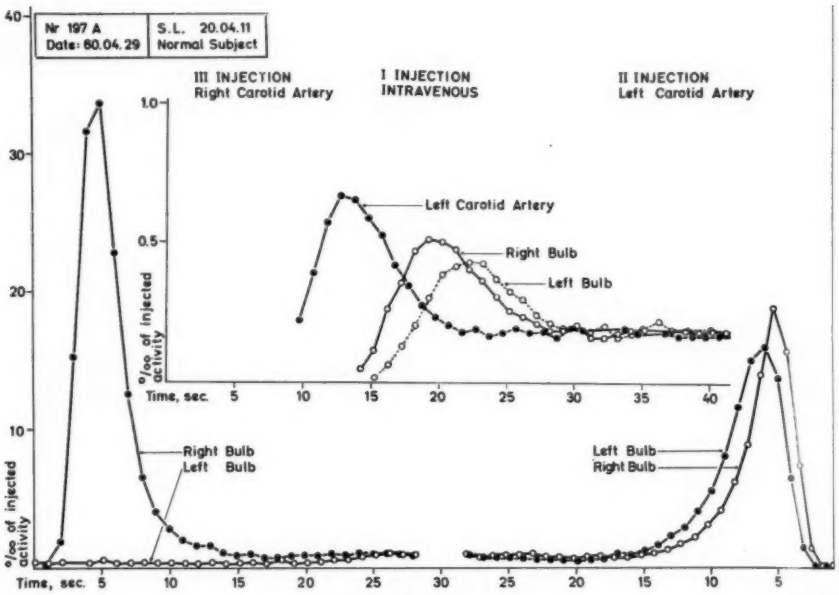


Fig. 18

40 years

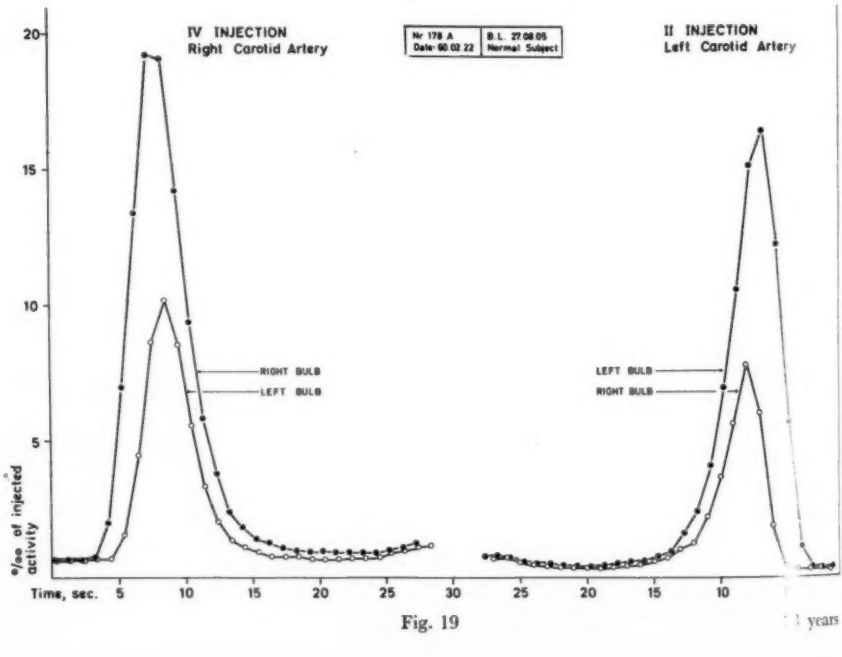


Fig. 19

years

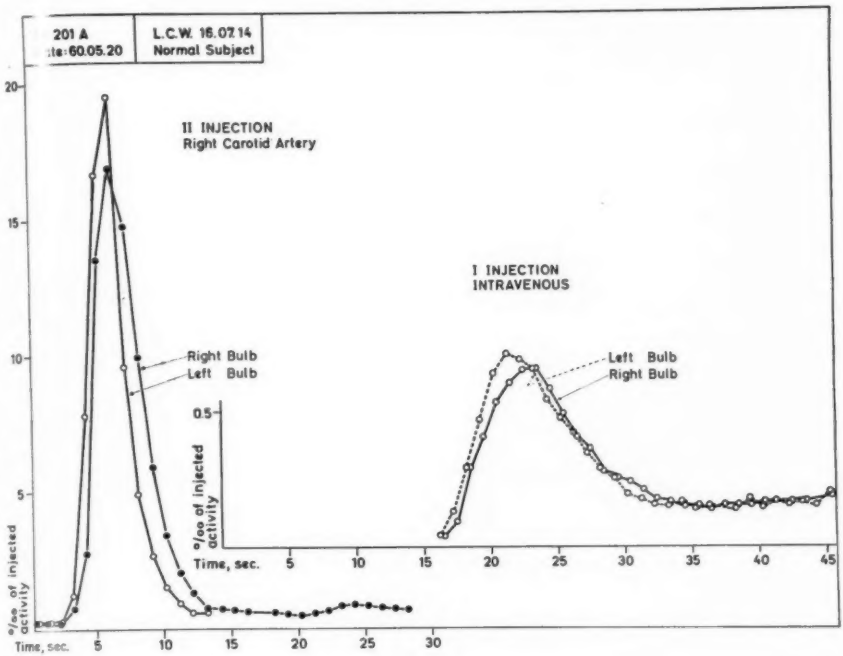


Fig. 20 44 years

Right car. art.:	Ipsilat. bulb	Contralat. bulb
App.	3 sec	3 sec
Peak	6 »	6 »
Disapp.	13 »	12 »

Cerebral blood flow 866 ml/min (10.4 % of cardiac output)
Cardiac output 8 300 ml/min
Total blood volume 5 380 ml
Heart volume 680 ml : 410 ml/m²

Legend for Fig. 18 (opposite page)

Right car. art.:	Ipsilat. bulb	Contralat. bulb	Left car. art.:	Ipsilat. bulb	Contralat. bulb
App.	2 sec	0 sec	App.	3 sec	2 sec
Peak	5 »	0 »	Peak	6 »	5 »
Disapp.	13 »	0 »	Disapp.	15 »	14 »

Cerebral blood flow 671 ml/min (8.2 % of cardiac output)
Cerebral pool volume 96 ml (1.5 % of total blood volume)
Cardiac output 8 200 ml/min — Total blood volume 6 512 ml
Mean circulation time 8.6 sec — Heart volume 850 ml : 390 ml/m²

Legend for Fig. 19 (opposite page)

Right car. art.:	Ipsilat. bulb	Contralat. bulb	Left car. art.:	Ipsilat. bulb	Contralat. bulb
App.	4 sec	5 sec	App.	4 sec	6 sec
Peak	7 »	8 »	Peak	7 »	8 »
Disapp.	16 »	15 »	Disapp.	15 »	14 »

Cerebral blood flow 971 ml/min — Total blood volume 5 240 ml — Heart volume 970 ml: 430 ml/m²

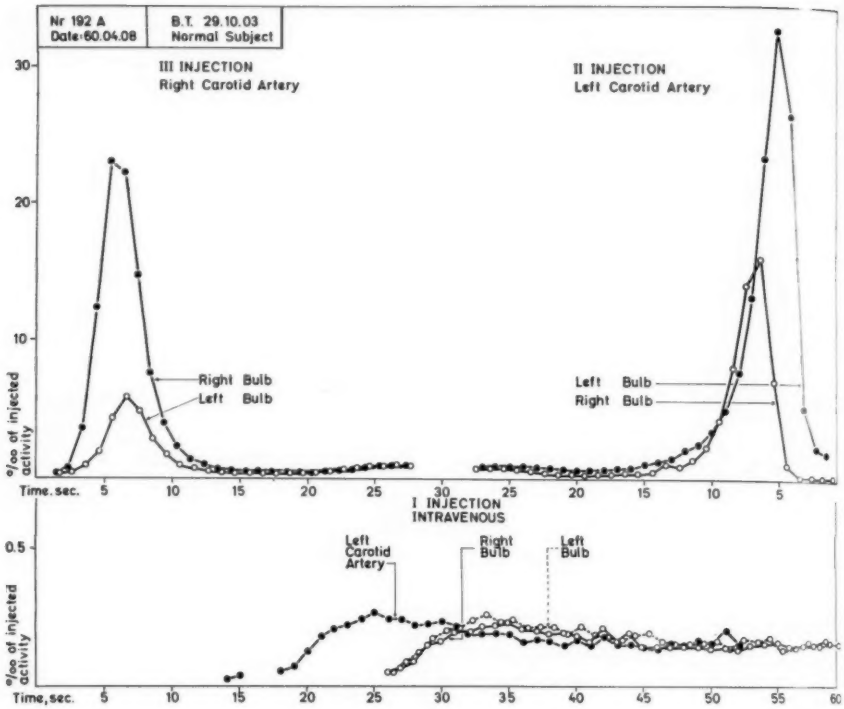


Fig. 21

31 years

Right car. art.:	Ipsilat. bulb	Contralat. bulb	Left car. art.:	Ipsilat. bulb	Contralat. bulb
App.	2 sec	4 sec	App.	2 sec	4 sec
Peak	5 »	7 »	Peak	5 »	6 »
Disapp.	14 »	13 »	Disapp.	17 »	14 »

Cerebral blood flow 791 ml/min (9.7 % of cardiac output)
Cerebral pool volume 91 ml (1.5 % of total blood volume)
Cardiac output 8 200 ml/min — Total blood volume 6 156 ml
Mean circulation time 6.9 sec — Heart volume 840 ml : 390 ml/m²

Legend for Fig. 22 (opposite page)

Right car. art.:	Ipsilat. bulb	Contralat. bulb	Left car. art.:	Ipsilat. bulb	Contralat. bulb
App.	2 sec	4 sec	App.	2 sec	3 sec
Peak	5 »	6 »	Peak	4 »	6 »
Disapp.	13 »	9 »	Disapp.	12 »	13 »

Cerebral blood flow 943 ml/min (15.5 % of cardiac output)
Cerebral pool volume 114 ml (3.5 % of total blood volume)
Cardiac output 6 100 ml/min — Total blood volume 3 265 ml
Mean circulation time 7.3 sec — Heart volume 410 ml : 280 ml/m²

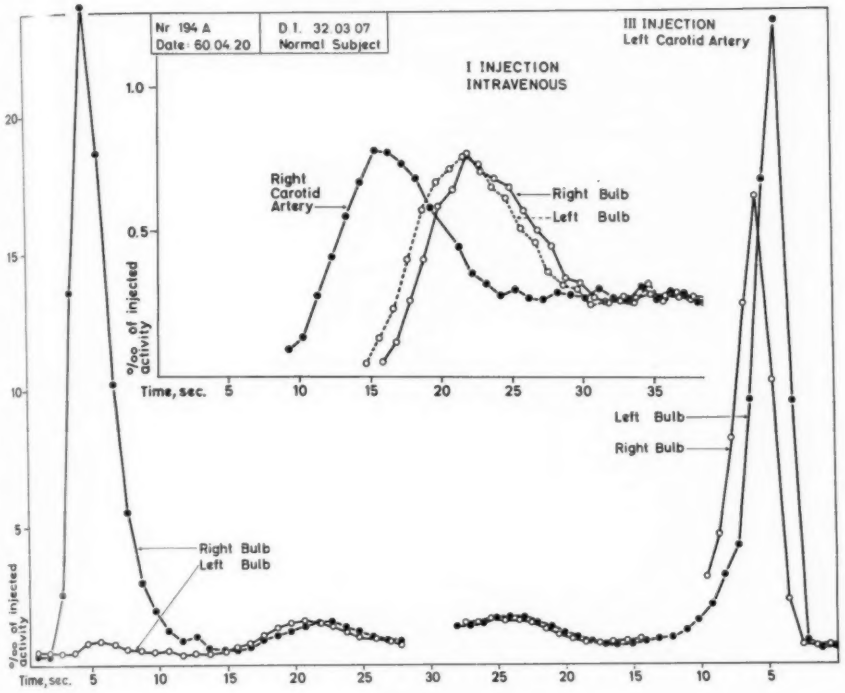


Fig. 22 28 years

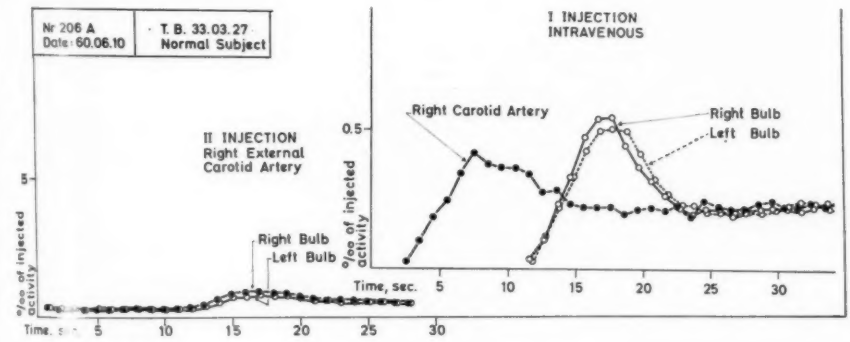


Fig. 23 27 years

Cardiac output 9 900 ml/min
Mean circulation time 4.8 sec

Total blood volume 4 267 ml
Heart volume 730 ml : 430 ml/m²

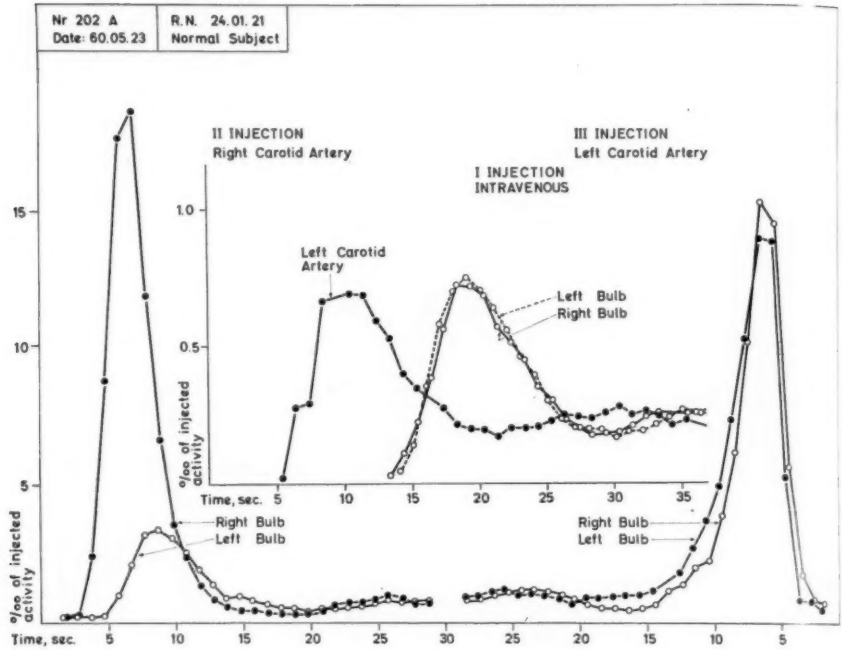


Fig. 24 36 years

Right car. art.:	Ipsilat. bulb	Contralat. bulb	Left car. art.:	Ipsilat. bulb	Contralat. bulb
App.	3 sec	5 sec	App.	3 sec	3 sec
Peak	7 »	9 »	Peak	6 »	6 »
Disapp.	14 »	15 »	Disapp.	15 »	15 »

Cerebral blood flow 948 ml/min (13.1 % of cardiac output)
Cerebral pool volume 152 ml (3.2 % of total blood volume)
Cardiac output 7 200 ml/min — Total blood volume 4 739 ml
Mean circulation time 9.6 sec — Heart volume 660 ml : 400 ml/m²

Acknowledgement

The support received for this work, grant H-3219, from the National Institute of Health U. S. Public Health Service is gratefully acknowledged. We also wish to thank Docent G. Porjé who has greatly facilitated our investigation.

SUMMARY

The cerebral blood flow, blood volume and circulation time through the brain were investigated with labelled radioactive erythrocytes in 34 healthy males. The time intervals of appearance, peak concentration and disappearance in the jugular bulbs were determined

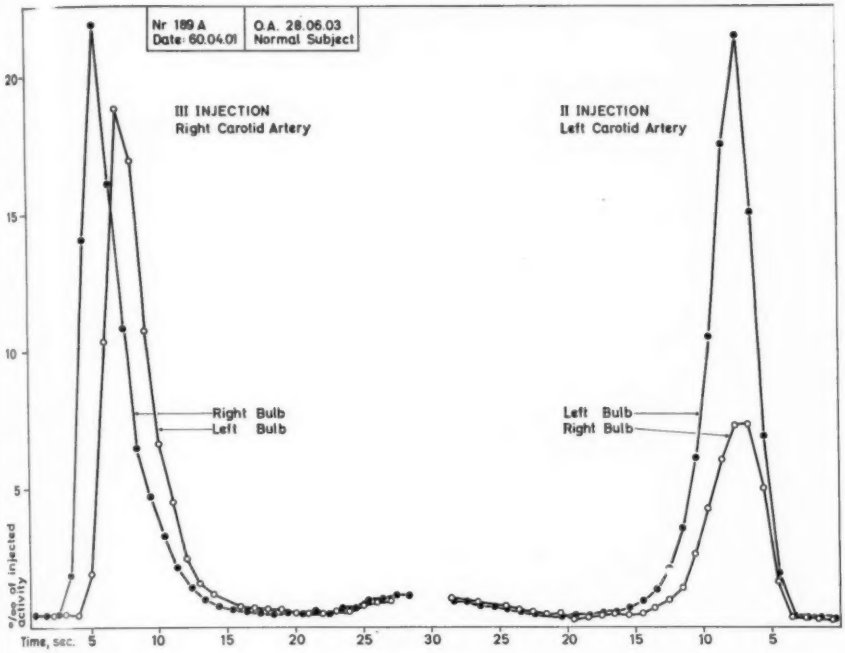


Fig. 25 32 years

Right car. art.:	Ipsilat. bulb	Contralat. bulb	Left car. art.:	Ipsilat. bulb	Contralat. bulb
App.	3 sec	5 sec	App.	4 sec	4 sec
Peak	5 »	7 »	Peak	7 »	7 »
Disapp.	14 »	16 »	Disapp.	15 »	14 »

Cerebral blood flow 781 ml/min — Total blood volume 4 997 ml — Heart volume 580 ml : 320 ml/m²

from dilution curves obtained after injection into the carotid arteries. The variations were found to be small and no correlation was obtained between the cardiac output and the cerebral blood flow or between the latter and the age of the subjects.

ZUSAMMENFASSUNG

Die zerebrale Blutzirkulation, die zerebrale Blutmenge und die Umlaufzeit des Blutes durch das Gehirn wurden mit radioaktiven Erythrozyten bei 34 gesunden Männern untersucht. Die Zeitabstände zwischen dem Auftreten, der höchsten Konzentration und dem Verschwinden in den jugularen Bulben wurden aus Verdünnungskurven nach Injektion in die AA. carotis bestimmt. Die Schwankungen sind bei normalen Personen offenbar sehr gering. Keine Korrelation wurde zwischen dem Herz-Minutenvolumen und dem zerebralen Blutzirkulation oder zwischen dem letzteren und dem Alter der Personen gefunden.

RÉSUMÉ

Le débit sanguin cérébral, le volume sanguin et les temps de circulation à travers le cerveau ont été étudiés sur 34 sujets masculins en bonne santé au moyen d'érythrocytes marqués radioactifs. Les intervalles de temps d'apparition, de concentration maximale, et de disparition dans les golfes des jugulaires ont été déterminés à partir des courbes de dilution après injection dans les artères carotides. Les variations semblent très minimes chez les sujets normaux. On n'a pas trouvé de corrélation entre le débit cardiaque et le débit cérébral, ni entre celui-ci et l'âge des sujets.

REFERENCES

ANDERSSON, B. J.: Studies on the circulation in organic systems with applications to indicator methods. Trans. Roy. Inst. Technology (Sthlm) (1957) No. 114.

EDWARDS, N. A.: Anatomic variations of the cranial venous sinuses. Arch. Neurol. Psychiat. 26 (1931), 801.

GREITZ, T.: Radiologic study of the brain circulation by rapid serial angiography of the carotid artery. Acta radiol. (1956) Suppl. No. 140.

HELPS, E. P. W. and MC DONALD, D. A.: Observations in laminar flow in veins. J. Physiol. 124 (1954), 124.

MONIZ, E.: Sur la vitesse du sang dans l'organisme. Ann. Méd. 32 (1932), 193.

NYLIN, G.: Estimation of cerebral blood flow and cerebral blood pool by aid of labeled erythrocytes. *In:* Cerebral vascular diseases. Ed. by Wright and Millikan. Grune and Stratton, New York 1958.

— and BLÖMER, H.: Studies on distribution of cerebral blood flow with thorium B-labeled erythrocytes. Circulat. Res. 3 (1955), 79.

— and HEDLUND, S.: Blood flow and pool in heart, lungs and brain. *In:* Circulation. Proc. Harvey Tercentenary Congress. Ed. by John Mc Michael. Blackwell's, Oxford 1958.

— — and REGNSTRÖM, O.: Studies of the cerebral circulation with labeled erythrocytes in healthy man. To be published in Circulation Res. (1961).

— BLÖMER, H., JONES, H., HEDLUND, S. and RYLANDER, C.-G.: Further studies on the cerebral blood flow with thorium B-labelled erythrocytes. Brit. Heart J. 18 (1956), 385.

— SILVERSKIÖLD, B. P., LÖFSTEDT, S., REGNSTRÖM, O. and HEDLUND, S.: Studies on cerebral blood flow in man, using radioactive-labeled erythrocytes. Brain 83 (1960), 293.

SCHURR, P. H. and WICKBOM, I.: Rapid serial angiography: Further experience. J. Neurol. 15 (1952), 110.

SHENKIN, H., HARMEL, M. and KETY, S.: Dynamic anatomy of the cerebral circulation. Arch. Neurol. Psychiat. 60 (1948), 240.

TÖNNIS, W. und SCHIEFER, W.: Zirkulationsstörungen des Gehirns in Serienangiogram. Springer Verlag, Berlin-Göttingen-Heidelberg 1959.

FRO THE RESEARCH LABORATORIES OF SCHERING A. G., BERLIN, DEUTSCHLAND.

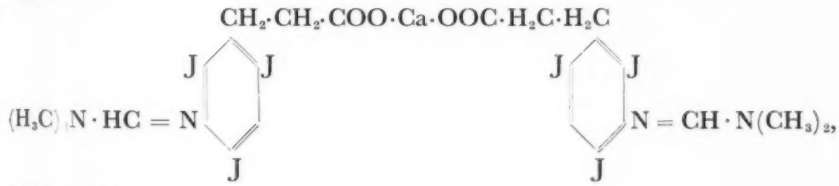
PHARMACOLOGICAL PROPERTIES AND EXCRETION KINETICS OF SOLU-BILOPTIN

by

K. H. KIMBEL and H. LANGECKER

The fact that Biloptin, like virtually all other compounds used for oral cholecystography and cholangiography, has a disagreeable taste prompted us to supply this new contrast medium (sodium-β-(3-dimethylamino-methyleneamino-2,4,6-triiodophenyl)-propionate) in capsules instead of tablets. It is well known that a certain percentage of patients, and especially those with gastrointestinal disorders, are unable to swallow capsules and we therefore decided to look for a tasteless derivative of Biloptin® (B) that could be administered in the form of a suspension. The calcium salt, Solu-Biloptin® (SB) which is sparingly soluble in water, surpassed all other tested compounds in this respect and surprisingly exhibited excellent roentgenographic properties besides being well tolerated (SALTZMAN).

Chemical properties (according to figures supplied by Dr W. Neudert). Calcium-bis-β-(3-dimethylamino-methyleneamino-2,4,6-triiodophenyl)-propionate



Submitted for publication 6 December 1960.

Table 1

Comparison of acute toxicity of B and SB, in mice weighing between 18 and 22 g, and rats weighing 100 to 120 g. LD_{50} was calculated according to KÄRBER.

Species	B = Sodium salt Route of administration			SB = Calcium salt Route of administration	
	Intravenous solution	Intraperitoneal solution	Peroral solution	Intraperitoneal suspension	Peroral suspension
Rat	0.3—0.4	0.37	2.8—3.2	0.43	1.5—3.0
Mouse	0.3	0.35	1.5	0.3	1.0

$C_{24}H_{24}J_6N_4O_4Ca$, has a molecular weight of 1 234 and an iodine content of 61.7 %. The colorless and slightly bitter-tasting microcrystalline compound melts at 298 to 302° C and has the following solubilities at 37° C: water 0.35 g 100 ml; normal saline (0.9 %) 0.46 g/100 ml; plasma ~ 2.3 g/100 ml; olive oil ~ 1.8 g/100 ml.

It is fairly soluble in $HCCl_3$ (in presence of traces of C_2H_5OH) and in glacial acetic acid, readily soluble in dimethyl formamide and dimethylsulphoxide, and insoluble in acetone and ether. Ultraviolet absorption: $\varepsilon_{264} = 25\,800$ and $\varepsilon_{234} = 74\,300$ (methyl alcohol); $\varepsilon_{236} = 71\,900$ (water).

Pharmacologic properties

Acute and chronic toxicity. In toxicity SB closely resembles the sodium salt (B). The LD_{50} of both compounds as determined in rats and mice are presented in Table 1.

SB seems to be slightly better tolerated in rats than B on intraperitoneal injection although the corresponding values in mice are identical. The subacute toxicity was tested in 10 rats (90 to 110 g bodyweight) receiving 8 doses of 200 mg SB/kg bodyweight as a 20 % suspension in gum acacia orally during 10 days. They gained about 30 % in bodyweight and looked normal. The same dose given to 10 rats of the same weight 15 times during 19 days did not change the normal weight increase of about 37 %. Microscopic examination of the liver and kidney did not reveal any pathologic changes; the same was true of the urine analysis. Three dogs weighing between 8.1 and 10.5 kg received 200 mg SB/kg bodyweight in capsules 14 times during 17 days and showed no signs of incompatibility nor changes in bodyweight, blood or urine.

Local compatibility. A saturated solution of SB in Tyrode's solution is well tolerated when injected intramuscularly in dogs (0.5 ml), rabbits (0.5 ml) and rats (0.1 ml); a subcutaneous injection of 0.1 ml into rabbits ear or guinea pigs abdomen produced no irritation. Instillation into the rabbit eye was also well tolerated.

Table 2

Excretion of labelled Biloptin (B) and Solu-Biloptin (SB) (prepared by Dr Schulze) in bile of rats, weighing between 100 and 120 g, after intraduodenal application of 100 mg/kg bodyweight of the compound. The figures represent percentages of the administered dose calculated from the I^{131} content in the bile.

Compound	Number of animals	0—1/2 hr	1/2—1 hr	1—2 hrs	2—3 hrs	3—4 hrs	Total
Solu-Biloptin[1]	18	7.1	14.0	26.2	17.4	9.3	74.0
Solu-Biloptin[2]	9	5.5	17.8	30.0	18.5	8.9	80.7
Biloptin[3]	12	6.3	15.7	32.0	18.3	9.6	81.9
Biloptin[4]	10	16.7		29.6	23.1	11.7	81.1

1) 2 % suspension in 10 % gum acacia.
2) In the form of the commercial preparation (4 % micronized suspension with some additives).
3) and 4) 2 % solution of the sodium salt.

Effects on circulation and respiration. Intravenous injections of 4 ml of a saturated solution of SB in Ringer's solution into cats anesthetized with Pernocton® did not change the blood pressure or respiration rate. In the isolated frog heart preparation (Straub) the lowest concentration which caused a bradycardiac and a negative inotropic effect was identical with that found for B (10^{-3}). Concentrations down to 10^{-5} induced a vasodilatation in the L-norepinephrine pretreated rabbit's ear vein.

Influence on smooth muscle. Concentrations down to $2 \cdot 10^{-5}$ were found ineffective in the isolated guinea pig small intestine; the $BaCl_2$ spasm was inhibited partially at $2 \cdot 10^{-5}$ and totally at 10^{-4}, the same concentration antagonizing the spasm induced by lentine and histamine. In the isolated rabbit small intestine, concentrations from 10^{-5} brought about a decrease in amplitude, while tone and frequency remained unchanged. In the rabbit uterus no effect was seen up to $1.5 \cdot 10^{-4}$. Beginning with $7.5 \cdot 10^{-5}$ the effect of epinephrine was inhibited.

Excretion kinetics

Experiments in rats. We have shown in an earlier paper (HARWART, KIMBEL, LANGECKER and WILLENBRINK (1959) that more than 80 % of a single intraduodenal dose of 100 mg B (sodium salt)/kg bodyweight is excreted within 4 hours in the bile of rats. This route of administration is required in bile fistula experiments in rats because of the impaired gastric peristalsis after laparotomy. Furthermore, larger variations in absorption which, due to different gastric evacuation time would occur after oral administration, are thus avoided. The results of these experiments are compared with similar

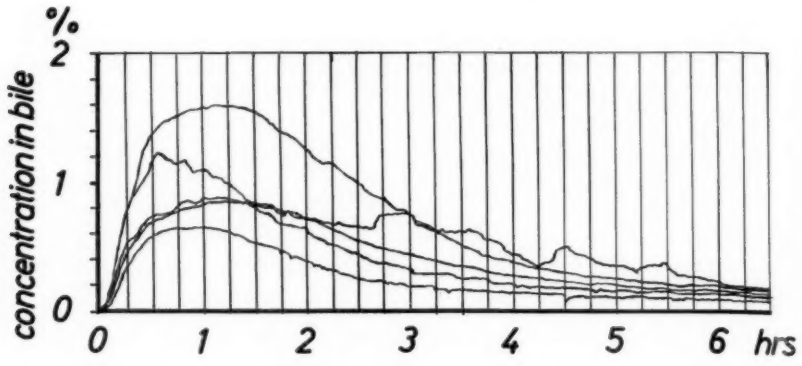


Fig. 1. Continuous recordings of radioactivity in bile fistula outflow of rats that received 100 mg/kg bodyweight of SB-I^{131} by intraduodenal injection at time 0. The system was calibrated by a 2 % solution of SB-I^{131}.

ones in bile fistula rats that received the same dose of SB as a suspension in gum acacia (18 animals) or in a micronized form (9 animals). It is evident from Table 2 that the rate of biliary excretion in rats is practically identical for both compounds.

With a new technique which has previously been described in detail (KIMBEL 1958) the absolute concentration of the opacifying element, i. e. the iodine concentration of a I^{131} labelled preparation, was recorded continuously in the bile passing the polythene tube of the bile fistula. From the five curves shown in Fig. 1 it is evident that the maximum of I^{131} concentration in the bile is attained between 30 and 90 minutes after administration, with values ranging from 0.6 to 1.6 % SB. The apparent discrepancy between these figures and the amounts excreted over the collecting periods in Table 2 which reach the maximum between 1 and 2 hours, may be explained by the fact

Table 3

Excretion of labelled B and SB in the bile of rats, weighing between 100 and 120 g, given in percentages of administered dose calculated from the I^{131} content in the bile after intravenous injection of 100 mg/kg bodyweight as sodium salt (B) or gum acacia suspension (SB).

	Animal No.	0—1/2	1/2—1	1—2	2—3 hrs	Total
Intravenous injection						
Solu-Biloptin	10	14.7	18.7	21.2	16.0	70.6
Biloptin	9		26.5	23.0	14.2	63.7
Injection into the portal vein						
Solu-Biloptin	5	8.6	13.9	19.6	16.4	58.5

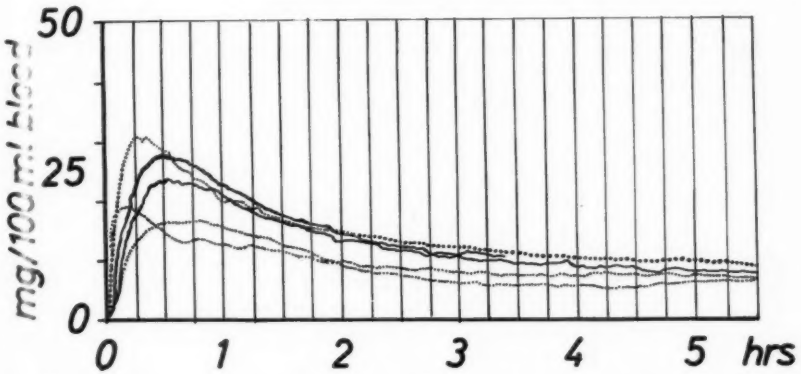


Fig. 2. Recordings of I^{131} concentration in the peripheral blood of albino rats weighing 200 to 250 g, measured in an extracorporeal shunt between the carotid artery and the external jugular vein of one side. Operation under ether anesthesia, experiment without anesthesia. The continuous curves represent Solu-Biloptin and the dotted curves Biloptin.

that in the latter method the integral over the observation time is shown while the continuous recording reflects the concentrations present in the bile over a very short time, limited only by the time constant inherent in the counting process and the chart recorder.

The intravenous injection of 100 mg SB (as a 2 % suspension in gum acacia) is well tolerated by rats and results in biliary excretion rates which closely resemble those obtained with B. From these results we have drawn the conclusion that the solubility of SB in blood at body temperature must be higher than in water, which has been confirmed by the solubility determinations given before. The excretion data are presented in Table 3.

Comparing the data obtained from the intraduodenal and intravenous administration it is surprising to find that there are differences only in the values for the first half hour, while the total output after three hours is of the same order. This observation speaks well for an excellent absorption of both compounds through the intestinal wall and was expected for the highly water soluble sodium salt. On the other hand the amount of water present in the rat intestine under normal conditions is not sufficient to dissolve 10 mg of the SB administered. Since the solubility of SB in 0.9 % saline at 37° C was found to be 0.46 %, 2.2 ml of saline would be necessary to dissolve this amount. In spite of the fact that, due to the continuous removal of the dissolved fraction of SB by absorption, the dissolution of the remainder would be facilitated, we would still have to find a slower absorption rate for SB. This, however, is not the case.

The excretion of SB in bile reflects the absorption process only indirectly.

Table 4

Absolute and comparable concentrations in portal vein blood of rats weighing between 225 and 250 g. The maximum values are underlined.

Time after injection	I^{131} concentration in portal vein blood of 2 rats after intraduodenal injection of 100 mg/kg bodyweight of SB-I^{131}				Ca^{45} concentration in portal vein blood of 4 rats after intraduodenal injection of 8.8 mg/kg bodyweight of $^{45}CaCl_2$, corresponding to the Ca content of SB			
min	1		2		1	2	3	
	mg %	% of dose/ml	mg %	% of dose/ml	% of administered dose/ml			
10	12.2	0.47	15.3	0.57	0.11	0.10	0.09	0.05
20	15.4	0.59	14.1	0.54	0.17	0.23	0.22	0.10
30	17.3	0.66	13.8	0.53				
40	13.5	0.52	11.4	0.44	0.26	0.28	0.27	0.13
50	12.8	0.49	11.8	0.45				
60	11.7	0.45	11.2	0.43	0.29	0.27	0.18	0.23

In order to obtain a closer insight into the absorption mechanism the blood level of I^{131} labelled SB was studied in the peripheral and portal vein blood. Fig. 2 shows that the continuously recorded level in the peripheral blood rises sharply a few minutes after the intraduodenal introduction of 100 mg SB/kg bodyweight attaining a maximum of 15 to 30 mg/100 ml within 30 to 60 minutes. The most important finding is the observation that, considering the biologic variation, there is no significant difference in the slope and maximum between the curves obtained for B and SB.

The concentrations in the portal vein blood which are given in Table 4 were calculated from individual samples taken every 10 minutes over a period of 1 hour. As regards their maximum the levels satisfactorily correspond with those found in the peripheral blood (Fig. 2). The absolute level in the portal vein blood was unexpectedly found to be lower than the arterial blood level. We may conclude from these experiments that the calcium salt SB and the sodium salt B are equally well absorbed by the rat intestine. In view of the poor solubility of the calcium salt in water this is rather surprising and may possibly be due to its transformation into a water soluble form, or to some special absorption mechanism, e. g. absorption via the lipoid phase or as particulate matter.

In an endeavour to study the first possibility SB was labelled with I^{131} as well as with Ca^{45}. If the unchanged calcium salt were absorbed, the specific activity would remain the same for I^{131} and Ca^{45}. In order to exclude the possibility that the Biloptin anion and the liberated Ca^{++} would have the same absorption rate, simulating the presence of unchanged SB, the Ca^{45} level in the portal vein blood was determined after the administration of an equivalent amount of $^{45}CaCl_2$ under comparable conditions. As demonstrated in Table 4 only 1/3 to 1/2 of an equivalent dose of $^{45}CaCl_2$ is absorbed.

Table 5

Excretion of Ca^{45} in the bile of rats, weighing from 100 to 130 g, after the intraduodenal administration of 10 mg/kg SB labelled with Ca^{45}, as 2 % suspension in 10 % gum acacia and an equivalent amount of $^{45}CaCl_2$ prepared in the same way, given as percentages of the administered dose.

Compound	Animal No.	0—1/2	1/2—1	1—2	2—3	3—4 hrs	Total
SB — Ca^{45}	10	0.2	0.5	0.6	0.4	0.2	1.9
	5	0.03	0.07	0.2	0.2	0.5	1.0
$^{45}CaCl_2$	5	0.28	0.20	0.22	0.16		0.9

Instead of a ratio of 1:1 for equimolar amounts of Ca^{++} and I^{131} Biloptin anion, the samples taken 20 minutes after intraduodenal administration showed ratios of 0.93, 0.69, 0.74, and 0.68. These figures indicate that during this interval a fraction of radioactivity represents a transformation product of SB which contains no Ca; 20 minutes later, i. e. 40 minutes after injection, the respective values are 0.88, 1.00 and 1.34 which means that most of the labelled material is now being absorbed in the unchanged form.

Besides the changes observed for B, which are discussed in the earlier cited report (HARWART, KIMBEL, LANGECKER, and WILLENBRINK) SB seems to undergo a further change in the liver, insofar as practically all the Ca is removed from the molecule. Hardly 2 % Ca^{45} of a dose of 100 mg/kg SB-Ca^{45} will be found in rat bile over a period of 4 hours compared with nearly 75 % of the I^{131} labelled compound. The data together with those from a control experiment in which equimolar amounts of $^{45}CaCl_2$ have been administered are presented in Table 5.

We roughly estimated the solubility of SB in olive oil in order to exclude an absorption via a solution in lipoid material present in the intestine and found that 5 ml of olive oil are not sufficient to dissolve 10 mg SB as used in rats. This finding excludes the possibility of its absorption in a dissolved form although it may still pass through the intestinal wall as an emulsion. In order to clarify the matter we administered 100 mg SB/kg to 5 rats with abdominal lymphatic fistulae (according to BOLLMANN) by intraduodenal injection. As shown in Table 6 the small amount of the compound present in the lymph cannot explain the good intestinal absorption of the SB. Furthermore, these results do not give an explanation for the lower SB level in the portal vein blood which might have been caused by an additional lymphatic transport.

Table 6

Transport of SB-I^{131} through abdominal lymphatics in 5 rats, weighing between 235 and 308 g, shown as percentages of the administered dose collected from abdominal lymphatic fistulas over a period of 24 hours.

	Animals numbered					Average
	1	2	3	4	5	
Per cent of administered dose ..	0.8	1.0	0.8	1.7	0.9	1.0

Table 7

Excretion of I^{131} in the bile and urine of 2 rabbits after intraduodenal injection of 100 mg labelled SB/kg bodyweight. At the beginning of the experiment the animals were given 50 ml water. After each withdrawal, the bladder was rinsed with 4 ml 0.9 % NaCl injected through an indwelling catheter. The figures represent the percentage cumulative excretion of the administered dose.

	Animal No.	0—1/4	0—1/2	0—1	0—2	0—3	0—4	0— 4 hrs
Bile	1	0.1	0.4	1.0	2.0	3.2	4.3	0.2
	2	0.1	0.2	0.6	1.3	1.7	1.9	4.3
Urine...	1	0.1	0.2	0.8	2.4	3.9	7.1	3.1
	2	0.8	1.4	2.3	5.0	8.4	10.4	8.6

Surveying our results with respect to the absorption mechanism of SB it may be stated that SB passes through the portal vein and is absorbed preferentially as a Ca salt. The mechanism facilitating its passage through the intestinal wall remains obscure but transport by the lipoid phase could be excluded. The assumption that solubilizing compounds in the intestinal juices are responsible for the fast absorption of SB is supported by an experiment in which we were able to demonstrate that SB has a solubility of about 90 % in rat intestinal juices of a pH of 6.7 to 7.0.

In accordance with the results obtained with B, the fraction of SB or its metabolic products excreted in the urine is small due to the rapid elimination of the compound via the bile. Three hours after the intravenous injection of 100 mg SB/kg, 4.2 % of the administered dose was found in the urine while 6.6 % was excreted within 4 hours after oral administration (animals Nos. 5 and 4 respectively, metabolic cage). Since in these experiments the flow of the bile into the intestinal lumen was not interrupted or deviated, an enterohepatic circulation cannot be excluded; however, in our experiments with the sodium salt (B) we have been able to show (HARWART et coll.) that reabsorption occurs to a minor degree only. In an experiment run over a period of 24 hours 31.1 % of the administered dose was found in the faeces and 19.6 % in the urine. From a clinical point of view it seems to be of interest that after ligature of the common bile duct in rats the urinary excretion within 4 hours was as high as 34.1 % of the dose administered by intravenous injection.

Table 8

Excretion of 100 mg SB/kg as a 2 % suspension in 10 % gum acacia given by stomach tube to 2 dogs. The iodine content of the bile and urine was determined chemically according to LANGECKER. *The figures represent the percentage of the administered dose.*

Animal No.	Excretion in bile		Excretion in urine	
	0—4 hrs	0—24 hrs	0—4 hrs	0—24 hrs
1	35	88	2.2	6.1
2	63	88.6	2.9	6.1

Table 9

Urinary excretion of 3 g SB in healthy volunteers. Figures calculated from the iodine content in urine, determined chemically according to LANGECKER.

Volunteer No.	Cumulative excretion in % of administered dose			
	0—2 hrs	0—4 hrs	0—8 hrs	0—24 hrs
1		16.6	23.4	48.4
	6.9	12.7	21.3	
2		9.0	21.7	46.7
	6.4	13.0	23.7	
3		8.9	27.9	42.2
4	5.8	12.6	28.1	
5	7.3	17.9	33.4	
6	8.3	13.4	23.2	
7	4.8	12.6	27.6	

Experiments in rabbits. It is generally recognized that rabbits are not the animals of choice in the evaluation of biliary contrast media. In an experiment with 2 animals weighing 2.1 to 2.2 kg the gallbladder was ligated during the preparation of an acute bile fistula. In one case the excretion of I^{131} in the urine was ten times as high as that in the bile while in the other animal the bile-urine coefficient was about 0.16. The reason for the different behaviour of rabbits necessitates further investigation (Table 7).

Experiments in dogs. Two dogs (13 kg and 16 kg) with a permanent bile fistula (according to the method of HARWART, KIMBEL, and LANGECKER (1959) received 100 mg SB/kg as a 2 % suspension in 10 % gum acacia orally. During a period of 24 hours both animals excreted 88 % of the administered dose in the bile. The figures are given in Table 8. The amount of iodine excreted within 4 hours in dog No. 2 agrees well with the data presented for rats.

Experiments in man. Since we had no opportunity of studying the excretion of SB in clinical cases of acute bile fistulae, we had to confine ourselves to the study of the excretion of SB in the urine of healthy volunteers. The data of the experiment in which 3 g SB were given orally to the fasting subjects in the early morning are presented in Table 9. It may be seen that 42—48 % was excreted in the urine within 24 hours. If we assume that the compound excreted in the bile is poorly reabsorbed, as it is in rats, we can deduce that about the same amount was excreted in the bile. When administered to clinical cases with abundant free gastric hydrochlorid acid the possible formation of Biloptin acid and its subsequent transformation into the sodium salt due to the alkaline reaction of the duodenum must be considered. A model experiment in which 1 mmol = 1.234 g SB were homogenized in 5 mmol 0.1 N HCl at 37° C for 10 min resulted in a transformation into the acid of about 55 %.

SUMMARY

Intestinal absorption, urinary and biliary excretion, toxicity and common pharmacologic properties of a tasteless derivative of Biloptin have been investigated in rats, dogs and man. It was found that Solu-Biloptin has the same favourable properties as Biloptin with respect to tolerability, absorption and biliary excretion. In spite of its poor solubility in water Solu-Biloptin is absorbed at least as quickly as Biloptin. An attempt is made to elucidate its absorption mechanism.

ZUSAMMENFASSUNG

Die Resorption im Darm, Ausscheidung in Galle und Harn, Toxizität und allgemeine pharmakologische Eigenschaften einer geschmacklosen, dem Biloptin verwandten Verbindung, wurde an Ratten, Hunden und beim Menschen geprüft. Es ergab sich, dass Solu-Biloptin die gleichen guten Eigenschaften wie Biloptin im Hinblick auf Verträglichkeit, Resorption und Gallenausscheidung aufweist. Trotz seiner geringen Wasserlöslichkeit wird es zumindest ebensogut resorbiert wie Biloptin. Es wurde versucht, den Resorptionsmechanismus von Solu-Biloptin aufzuklären.

RÉSUMÉ

Les auteurs ont étudié sur le rat, le chien et l'homme l'absorption intestinale, l'excrétion urinaire et biliaire, la toxicité et les propriétés pharmacologiques usuelles d'un dérivé insipide du Biloptin. Ils ont constaté que le Solu-Biloptin est aussi bien toléré, absorbé et excrété par voie biliaire que le Biloptin. Malgré sa faible solubilité dans l'eau, le Solu-Biloptin est absorbé au moins aussi vite que le Biloptin. Les auteurs se sont efforcés d'élucider le mécanisme de son absorption.

REFERENCES

Bollman, J. L., Cain, J. C. and Grindlay, J. H.: Techniques for the collection of lymph from the liver, small intestine or thoracic duct of the rat. J. Lab. Clin. Med. 33 (1948), 1349.

Harwart, A., Kimbel, K. H., und Langecker, H.: Die Beurteilung von Resorption und Ausscheidung der Gallenkontrastmittel. Arch. exper. Path. Pharm. 230 (1957), 367.

— — — und Willenbrink, J.: β-(3-dimethylamino-methylen-amino-2,4,6-trijodphenyl)-propionsäure als Gallenkontrastmittel. Arch. exper. Path. Pharm. 237 (1959), 186.

Kimbel, K. H.: Vorteile radioaktiv markierter Substanzen bei Clearance- und Verteilungsversuchen. 3. Sympos. Radioisotope in Klinik und Forschung. Urban u. Schwarzenberg, München u. Berlin 1958.

Langecker, H.: Die Verbrennung von Körperflüssigkeiten in Sauerstoffatmosphäre und ihre Anwendung zur Jodbestimmung in kontrastmittelhaltigen Flüssigkeiten. Klin. Wschr. 37 (1959), 471.

Saltzman, G.-F.: Solu-Biloptin (SH 550) as a contrast medium for peroral cholegraphy. Acta radiol. 54 (1960), 417.

FROM THE INSTITUTE OF RADIOPHYSICS (DIRECTOR: PROF. R. M. SIEVERT), KAROLINSKA SJUKHUSET, STOCKHOLM, SWEDEN.

CONDENSER CHAMBER DOSEMETER FOR RADIATION MEASUREMENT AT LOW DOSE RATE

by

R. THORAEUS

The radiation hazards to which workers may be subjected in various types of radiologic work are today extensively studied and discussed. The discussion is based more or less on radiation measurements made by monitoring the radiation received by the individual workers. In papers on such measurement results, the properties of the instruments used are however not always given and the reader is thus unable to assess the accuracy and reliability of the results.

One of the most dominant practical difficulties connected with protection in radiologic work is the fact that the radiation is only gradually attenuated by matter. This means that total protection cannot be obtained with a finite thickness of any material. The dimensions of protective barriers will thus include consideration of levels.

In general, when radiation interacts with matter, the energy of the beam will primarily be converted into motion of electrons. It is these electrons which, for example, are biologically efficient. The process by which the electrons are set in motion is however very complicated. In addition, the interaction is connected with emission of scattered radiation and, as this has lower energy than the primary, the total radiation will have a spectral distribution extended, more or less, in the direction towards lower energy. The spectral distribution after the interaction is consequently not the same as it was before; the radiation

Submitted for publication 21 September 1960.

quality is degraded. It is therefore of importance to use measuring instruments the energy dependence of which is small enough to permit safe measurements, even if the quality (spectral distribution) of the radiation is insufficiently known. Reference may be made to the NBS Handbook 51 (2) in which paragraph 11.8 runs as follows: 'All instruments for general use should be checked for energy dependence with gamma radiation from Ra or Co 60 and with X rays. There should not be more than a 20 per cent variation between 100 keV and 2 MeV.' Further instrument requirements will be found in paragraphs 16 to 19 of the same handbook.

The radiation behind protective barriers is usually not coming from a defined direction. The scattered radiation, for example, is arising from the whole irradiated volume of matter, and is thus very diffuse. This condition necessarily requires that the radiation detector (ionization chamber) has a sufficiently small direction dependence.

There are, finally, two fundamental conditions in the use of ionization chambers: the dose rate must be fairly constant over the volume occupied by the chamber, and the chamber must be completely irradiated. The last mentioned condition excludes, for example, narrow beams from being measured by chambers the size of which is greater than the cross-section of the beam.

Exposure dose measurement of low dose rate roentgen radiation in terms of the international roentgen by inclosed ionization chambers was discussed by the author in a previous paper (4). The design and properties of some condenser dosemeters provided with such chambers were then described. One of these instruments, designed and constructed by the author as early as 1943, is of particular interest as having a very high sensitivity, yet being of a reasonable size so that it may be conveniently used in both laboratory work and practical inspection. Its ionization chamber is cylindrical, about 15 cm in length and 7.5 cm in diameter, and is provided with a hollow inner electrode, 0.8 cm in diameter. It has an enclosed air volume of about 563 cm^3, and a total electrostatic capacitance of about 4 cm. The reader is referred to the quoted paper for further details.

This cylindric chamber was found to have sufficiently small direction and energy dependencies. It was extensively calibrated against a special chamber, a so-called drum chamber previously described by the author (3). The drum chamber in turn was directly calibrated against our free-air standard chamber in the region of 10 to 165 kV tube voltage; in this same region the variation of its calibration factor was only plus or minus 2.5 per cent.

The calibration result of the cylinder chamber is quoted in Table 1. Primary radiation as well as secondary radiation scattered from a wax phantom were used in the calibration. The result does not show any systematic changes of sensitivity due to quality of the radiation, and we may therefore be justified in using the average value $k = 25.5$ μr per volt. When this value is used over the whole range of radiation qualities investigated, the maximum error intro-

Table 1

Calibration results of chamber without added cap

Additional filter mm*	Tube voltage	Calibration factor in μr per volt	Radiation used
7 Pb	400 kV half-wave	26.3	Primary radiation obtained with tube voltage and filtration given
1 Pb	165 kV const.potential	25.7	
Tin filter	165 »	25.3	
0.5 Cu	165 »	25.7	
4 Al	145 »	25.6	
1 Al	100 »	25.2	
0	70 »	25.6	
0	50 »	24.5	
0	50 kV const.potential	26.2	Secondary radiation from a wax phantom irradiated by a primary beam obtained with tube voltage and filtration given
0	40 »	25.0	

Average factor 25.5 μr per volt $\pm$ 3.5 per cent

* The inherent filtration of the roentgen tube used at 400 kVp was equivalent to 0.6 mm Cu. At the remaining tube voltages another tube was used the inherent filtration of which was equivalent to only 0.95 mm Al.

duced will only be plus or minus 3.5 per cent, even if no details of the radiation quality are known. In regard to the wide range of qualities used this error may be considered relatively small. It may also be compared with accordant observations showing that a change of 5 per cent in the radiation received usually does not perceptibly affect the biologic reactions of the human body.

It may be worth mentioning that the sensitivity of the cylindric chamber was later directly calibrated against our free-air standard chamber at a tube voltage of 100 kV and an added filter of 4 mm of copper. The factor obtained was 25.0 μr per volt. This value may be compared with the value of 25.2 μr per volt given in Table 1 for 100 kV and a total filtration of about 2 mm of aluminium. The difference is only 0.8 per cent.

It appears further from Table 1 that three calibration factors have been obtained at 165 kV tube voltage, using the three added filters 0.5 Cu + 1 Al, normal tin filter, and 1 mm Pb. The average of the three factors is 25.6 μr per volt, and they all lie within the limits plus or minus 0.8 per cent. These observations show that the calibration factor is not affected by the great changes of spectral distribution obtained by such very different filtrations.

Due to these properties and to those shown in the previous paper (4), as well as to its reliable and stable performance, this cylinder chamber dosemeter has long been used by the standard laboratory as a substandard against

Table 2

Calibration results of chamber with cap

Primary radiation obtained with the tube voltages given below	HVL in mm Cu of the radiation used	Calibration factor in μr per volt
100 kV	0.1	26.5
140 »	0.35	26.0
175 »	0.9	25.5
200 »	2	25.0
280 »	4.4	25.2
Ra-γ	13.3	25.2

Average factor 25.6 μr per volt $\pm$ 2.9 %

which other instruments for inspection of protection are calibrated. In addition, two such instruments are used by the radiation protection inspection section of this institute for checking the sensitivity of their routine instruments. Measurements of the exposure dose rate at a sufficient number of suitably selected positions is the first and usual way of obtaining a survey of the radiation field caused by a radiation emitting source. Dosemeters of the type described above have, in fact, also proved to be very suitable for such surveying.

However, the increasing use of high energy radiation, for example gamma radiation, has raised the question as to whether the cylindric substandard can be used also in this region. It would then be necessary to provide the chamber with a complete enclosure of a suitable material to be sure that equilibrium ionization is measured. For this purpose a cylindrical enclosure of plexiglas was constructed. Its function is the same as that of the graphite cap used with the thimble chamber substandard previously described (1), viz. to provide equilibrium wall thickness. Readings were then taken with and without this enclosing 'cap', using roentgen radiation of tube voltages of 100 to 280 kV, and gamma radiation from the radium standard previously described (5). The exposure dose rate measurement of this radium gamma radiation is based on the substandard also previously described (1, 6), and its calibration against four national free-air standard chambers in the region of conventional roentgen radiation and against the cobalt 60 gamma radiation standard of the National Bureau of Standards, Washington, USA. The calibration factors of the cylindric substandard thus obtained are collected in Table 2. The average of the factors in μr per volt is 25.6 $\pm$ 2.9 per cent, which is very nearly the same as that given above for the chamber without cap.

It appears that at 100 kV and the light filtration resulting in a half-value layer of only 0.1 mm Cu, the attenuation in the added cap just begins to raise the calibration factor perceptibly. Checks taken in the region 50 to 70 kV and using a total filtration of only about 1 mm Al, have shown that the factor of the

substandard with cap is then 7 to 10 per cent higher than that without cap. To avoid impairment of the accuracy the added cap should accordingly not be used when radiations of energies below 100 kV are to be measured. However, if we permit a total variation in energy dependence of $\pm$ 7 per cent, i. e. well within the recommendations in the NBS Handbook 51 (2), the substandard with cap and with an average factor of about 26.5 μr per volt may be used over the whole energy region from 50 kV and practically to the present upper limit of the official validity range of the roentgen, without any particular knowledge of the radiation quality being required. Such a decrease of the measurement accuracy may be accepted when only approximative values are required, for example in preliminary studies of a radiation field, but not in calibration work in a standard laboratory.

The calibration factors shown in Tables 1 and 2 indicate a rather high sensitivity suitable for measurement of radiations of very low dose rate. However, when instruments of considerably lower sensitivity are to be calibrated, it is of great value to be able to reduce the sensitivity of the substandard. This can readily be accomplished by adding a suitable capacitor; this increases the electrostatic capacitance of the unit but does not alter the percentage change of calibration factor with radiation quality. Such a capacitor with amber as the dielectric medium is available for this purpose. It changes the calibration factor of the unit from 25.5 to 680 μr per volt, i. e. an increase of the factor by 26.6 times. The sensitivity is then suitable for calibration of instruments having measurement ranges of 50 to 250 mr.

SUMMARY

A cylindric condenser chamber dosemeter for exposure dose measurement of low dose rate radiations and its calibration results are described. As the chamber has a very low energy dependence it can be used with the same average calibration factor for radiations of energies from 40 kV and practically up to the present upper limit of the official validity range of the international roentgen unit.

ZUSAMMENFASSUNG

Ein zylindrischer Kondensatorkammerdosismesser für Messung von Bestrahlungsdosen von Strahlen mit geringer Dosisleistung sowie die Ergebnisse der Kalibrierung dieses Apparates werden beschrieben. Da die Kammer eine sehr kleine Energieabhängigkeit hat, kann er mit dem gleichen durchschnittlichen Kalibrierungsfaktor für Strahlungsenergien von 40 kV und praktisch bis zur gegenwärtigen oberen Grenze des offiziellen Gültigkeitsbereichs der internationalen Röntgeneinheit benutzt werden.

RÉSUMÉ

L'auteur décrit une chambre condensateur dosimètre cylindrique pour la mesure de dose d'exposition pour des radiations à faible débit de dose et donne les résultats de son étallonage. Comme ce dosimètre est très peu dépendant de l'énergie, il peut être utilisé avec le même facteur moyen d'étalonnage pour des radiations dont l'énergie va de 40 kV jusqu'à pratiquement la limite supérieure actuelle du domaine officiel de validité de l'unité roentgen internationale.

REFERENCES

1. HULTBERG, S., DAHL, O., THORAEUS, R., VIKTERLÖF, K. J. and WALSTAM, R.: Kilocurie cobalt 60 therapy at the Radiumhemmet, Chapter III. Acta radiol. (1959) Suppl. No. 179.
2. RADIOLOGICAL MONITORING METHODS AND INSTRUMENTS. NBS Handbook 51 (1952).
3. THORAEUS, R.: A small ionization chamber able to serve as a portable substitute for a standard chamber. Acta radiol. 22 (1941), 260.
4. — Quantitative meaurements of low dose-rate roentgen rays in terms of the international r-unit by closed ionization chambers. Ark. Fys. 4 (1951), 353.
5. — Periodic control of the function and constancy of ionization chamber dosemeters. Acta radiol. 45 (1956), 503.
6. — A substandard condenser dosemeter and its calibration against four national free-air standard chambers. Acta radiol. 48 (1957), 473.